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CHEMOSURGICAL TREATMENT OF CANCER OF THE FACE

A Microscopically Controlled Method of Excision

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THE DEVELOPMENT of the chemosurgical method has been described,[1] as has the use of the method in the treatment of cancer in specific sites such as lip,[2] nose,[3] ear [4] and eyelid.[5] This article concerns the chemosurgical treatment of cancer of the face, exclusive of the nose, ear, eyelid and vermilion portion of the lips.

TECHNIC

The most important feature of the chemosurgical treatment of cancer is the microscopic control of excision afforded by the technic hereinafter described.

As the term "chemosurgery" suggests, the tissues are chemically treated and then surgically excised. The chemical treatment serves to produce fixation of the tissues, so that specimens may be excised for systematic microscopic examination.

To illustrate the technic there will be described the chemosurgical treatment of a simple squamous cell epithelioma of the temple (fig. 1*A*).

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1. (*a*) Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Research **1**:49 (Jan.) 1941. (*b*) Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, Arch. Surg. **42**:279 (Feb.) 1941.

2. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Lip: A Microscopically Controlled Method of Excision, Arch. Surg. **48**:478 (June) 1944.

3. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Nose: A Microscopically Controlled Method of Excision, Arch. Surg. **53**:327 (Sept.) 1946.

4. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Ear: A Microscopically Controlled Method of Excision, Surgery **21**:605 (May) 1947.

5. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Eyelid: A Microscopically Controlled Method of Excision, Arch. Ophth., to be published.

The following steps were taken: 1. Dichloroacetic acid was applied to the portion of the mass covered with skin. Whitening of the skin indicated adequate penetration of the keratin, which is a barrier to the passage of zinc chloride. 2. Zinc chloride fixative paste[6] was applied in a depth of about 2 mm. 3. The treated area was covered with cotton and then with an overlapping cotton dressing spread with petrolatum to make a moisture-tight closure. 4. On the next day part of the cancer was excised (first excision, fig. 2 *A*). The incision was made through the deeper portion of the fixed tissue but not through living tissue, so that no pain or bleeding was caused by this operation. The cancer at this level was grossly visible as white crumbly tissue, so the fixative was reapplied in a depth of approximately 0.5 mm. 5. The next day a second layer of tissue was excised. Since

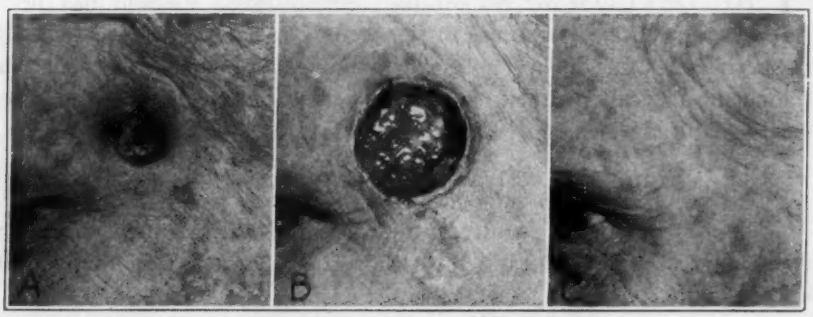

Fig. 1.—*A*, squamous cell epithelioma. *B*, granulation tissue ten days later, after the cancer had been excised in three stages (see fig. 2) and after the final layer of fixed tissue had separated. *C*, healed lesion. The patient was free of cancer when she died of other causes after eight years.

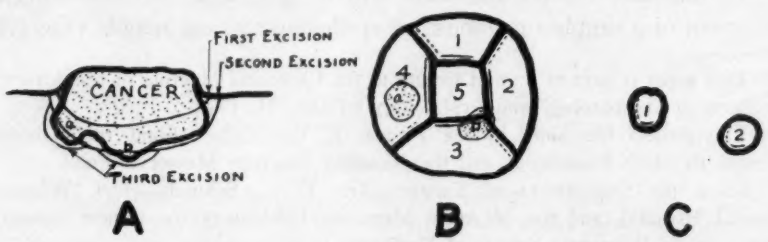

Fig. 2.—Diagram illustrating the chemosurgical technic as used in the treatment of the lesion pictured in figure 1. *A*, vertical cross sectional view showing the levels of the three excisions and the position of the two outgrowths, *a* and *b*, from the main cancerous mass. *B*, map of the five specimens which comprised the second excised layer. Microscopic examination of the frozen sections cut through the under surface of each of these specimens revealed cancer in the stippled areas. These areas of cancer corresponded to downgrowths *a* and *b* in *A*. *C*, map of the specimens from the third excision. Cancer was not present.

cancerous tissue was not grossly visible at this level, the excised layer was divided into five specimens of convenient size (fig. 2 *B*), their edges were marked with merbromin (solid lines) and ordinary bluing (dotted lines) for orientation, and

6. The zinc chloride fixative paste contains 40 Gm. of stibnite (80 mesh sieve), 10 Gm. of powdered sanguinaria and 34.5 cc. of a saturated solution of zinc chloride

frozen sections were cut through the under surface of each specimen. Scanning of the sections under the microscope revealed two areas of cancer, *a* and *b*, corresponding to downgrowths *a* and *b* in the vertical view (fig. 2*A*). 6. Further application of the fixative was limited to these two areas. 7. The next day a cancer-free plane was reached (fig. 2*C*). The wound, which was covered with a thin layer of fixed tissue, was dressed with a cotton dressing spread with petrolatum to avoid drying. 8. One week later the final layer of fixed tissue had loosened, so that it easily was dissected off with sharp-pointed scissors. 9. The granulation tissue (fig. 1*B*) was covered with scarlet red ointment-impregnated gauze over which a cotton dressing was placed. The wound healed in three weeks with a flat soft smooth scar which, though pink at first, faded to the color of the surrounding skin (fig. 1*C*).

The average time in which the final layer of fixed tissue separates from living tissue varies for different areas of the face (table 1). There may be individual variation of two or three days above or below these average figures.

TABLE 1.—*Average Time Required for Separation of Final Layer of Fixed Tissue in Various Regions of the Face*

Region	Average Number of Days
Chin	5.8
Forehead	6.5
Upper lip (skin)	6.6
Cheek	7.2
Neck	8.4
Temple	8.8
Scalp	10.5

Cancerous involvement of periosteum and even of the bone itself may occur, particularly in regions where the skin closely overlies the bone, as on the forehead, scalp, temple and upper part of the cheek. The chemosurgical technic readily may be used to trace out cancer in the periosteum, but, of course, it is not feasible to make frozen sections of the bone itself. Fortunately, bone often bars the deep extension of cancer for a long period, and when involvement of bone does occur the erosion is grossly visible. Chemical fixation of bone is easily accomplished by means of zinc chloride though the penetration is slower than through soft tissues, and instead of the scalpel the tools used are the rongeur and chisel. When there is doubt as to the nature of the tissue causing the honeycombing of the bone, frozen sections may be made of the bits of soft tissue dissected from the bone. The separation of chemically fixed bone requires about three weeks unless it has received roentgen or radium irradiation, in which case separation is delayed.

Cancerous erosion through the skull with involvement of the underlying membranes and brain does not necessarily contraindicate the continuation of chemosurgical treatment unless the diameter of the defect in the skull exceeds 4 cm. or unless a vital area of the brain is involved.

Thus, a considerable amount of tissue from the frontal lobe may be removed without ill effects, but great care must be exercised to avoid entrance into the anterior horns of the lateral ventricles. The rapid penetration of the fixative through tissue of the brain necessitates the reduction of the amount of fixative applied. Fixed cerebral tissue separates in about seven days and granulation tissue forms, providing a base for rapid epithelization.

While hemorrhage ordinarily is not a problem, precautions are indicated when the cancer involves regions containing large vessels. Vessels such as the external maxillary and the superficial temporal arteries may require the placement of suture ligature in the wound. If the carotid arteries are thought to be involved, a ligature at a level below the wound is placed before chemosurgical treatment is begun.

Involvement of the temporomandibular joint by deep-seated carcinoma may necessitate destruction of that structure. Ankylosis has not ensued in any case of this type in which the chemosurgical technic was used. However, some degree of malocclusion may occur.

Deep cancerous invasion in the path of the seventh cranial nerve may necessitate interruption of the nerve during chemosurgical excision. However, the conservatism made feasible by the method makes possible the preservation of a maximum amount of nerve tissue. In some cases in which a relatively small segment of a nerve has been interrupted during chemosurgical treatment, there has been a return of function after a year or so.

THERAPEUTIC RESULTS IN CASES OF BASAL CELL EPITHELIOMA OF THE FACE

Two hundred and thirty-two basal cell epitheliomas of the face were chemosurgically treated during the seven and one-half years ending Jan. 27, 1944, which date is three years prior to this writing. The cancers were in all stages from early to far advanced. Over a third of the patients previously had been unsuccessfully treated by operation or irradiation. There were no metastases.

End Results After Three Years or More.—The 232 cases observed for three years or more were divided into "indeterminate" and "determinate" groups according to the plan of Martin, MacComb and Blady.[7] The indeterminate group included the cases of 49 patients who died of intercurrent disease before the expiration of the three year period without evidence of cancer and the cases of 9 patients who were lost from observation without evidence of cancer when last seen. The determinate group included the unsuccessful results, of which there were none, and the 174 successful results.

7. Martin, H. E.; MacComb, W. S., and Blady, J. V.: Cancer of the Lip, Ann. Surg. **114**:341 (Sept.) 1941.

Thus, in the three year period successful results were obtained in 100 per cent of the 174 cases in the determinate group.

End Results After Five Years or More.—In the group of 137 cases observed for five years or more there were 43 cases in the indeterminate group and 94 cases in the determinate group. In the five year period successful results were obtained in 100 per cent of the 94 cases of the determinate group.

Fig. 3.—*A*, basal cell epithelioma of group D. *B*, granulation tissue after the cancer had been excised in four microscopically controlled stages and after removal of the final layer of fixed tissue. *C*, healed lesion. The patient is free of cancer after three and one-half years.

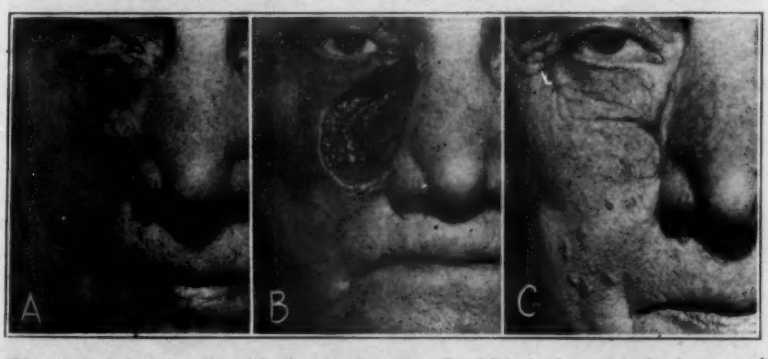

Fig. 4.—*A*, basal cell epithelioma of group C which had recurred after surgical excision seven years before. *B*, granulation tissue after separation of final layer of fixed tissue. The cancer had extended superiorly for an unsuspected distance. *C*, healed lesion. The patient was free of cancer when she died of an accident after over two years.

Effect of Size of Lesion on Prognosis.—In the 174 cases in the determinate group in the three year period, the lesions were divided into four groups according to their average diameter as measured at the initial clinical examination: A, under 1 cm.; B, 1 to 2 cm.; C, 2 to 3 cm. (figs. 4 and 6) and D, 3 or more cm. (figs. 3 and 5).

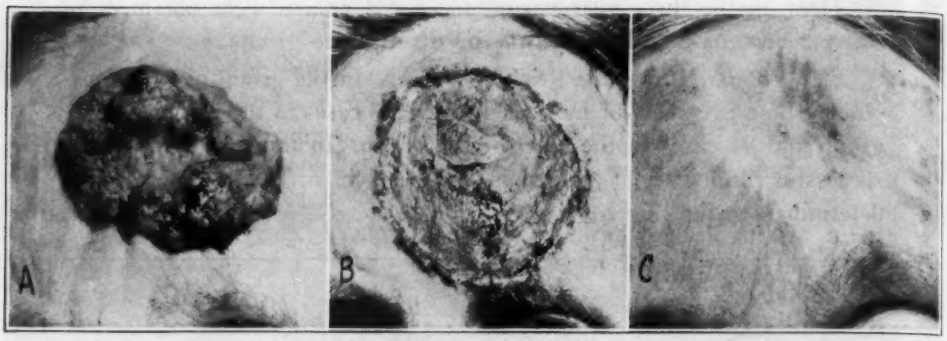

Fig. 5.—*A*, basal cell epithelioma of group D. *B*, granulation tissue and area of exposed skull after removal of final layer of fixed tissue. The layer of fixed bone was removed eleven days later. *C*, healed lesion. The patient was free of cancer when she died of other causes after over three years.

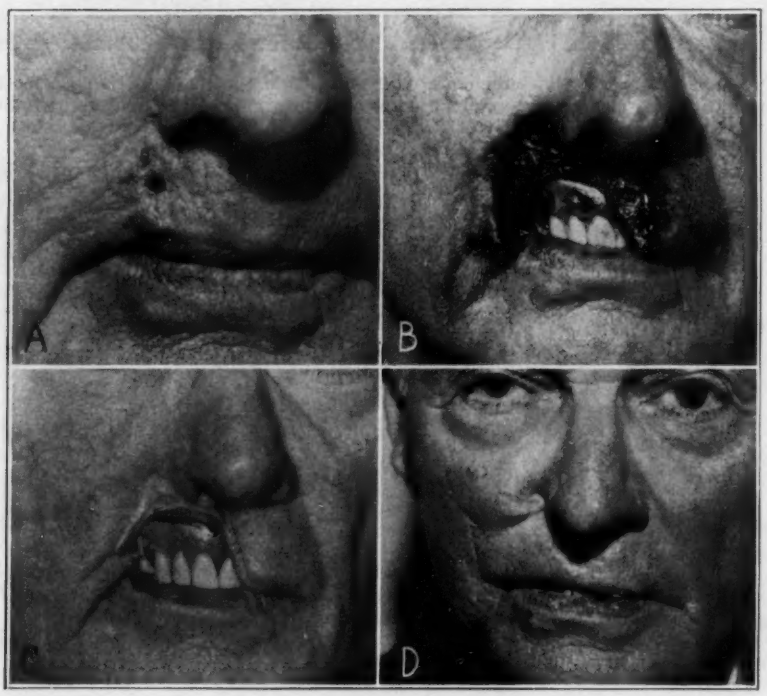

Fig. 6.—*A*, basal cell epithelioma of group *C* which had recurred after caustic and roentgen ray treatment. *B*, granulation tissue and defect after chemosurgical removal of the cancer in seven microscopically controlled stages. The neoplasm involved much more tissue than the original appearance would indicate. *C*, defect after healing. *D*, appearance after plastic repair by Dr. V. B. Hyslop. The patient is free of cancer after five years.

While 59 of the lesions were under 1 cm. in average diameter, a much larger number were of larger size (table 2). Inasmuch as all of the lesions, regardless of size, were successfully treated, it may be concluded that the size of the lesion is not an appreciable factor in the determination of prognosis. This is not to imply, however, that all basal cell epitheliomas of the face can be cured by means of the chemosurgical method. Obviously, if a cancer should extensively involve vital structures, such as certain portions of the brain or the internal carotid and jugular vessels, the neoplasm might become incurable despite the microscopic control of the chemosurgical method.

Effect of Previous Treatment on Prognosis.—Of the 174 cases in the determinate group in the three year period there were 60 (34.5 per cent) in which the patients had previously received unsuccessful treatment by operation, irradiation or caustics. All the 60 recurrent lesions, as well as the 114 lesions for which the patients had not received previous treatment, were cured by means of chemosurgical treatment.

TABLE 2.—*Distribution of Basal Cell Epithelioma According to Size*

Group	Average Diameter, Cm.	Number of Lesions
A	Under 1	59
B	1-2	58
C	2-3	31
D	3 or more	26
All groups		174

The high curability of recurrent basal cell epitheliomas of the face by means of chemosurgical excision is in contrast to the low curability of such lesions by other methods.

Effect of Degree of Malignancy on Prognosis.—It is convenient to classify basal cell epithelioma into two groups, "invasive" and "noninvasive," to provide a rough indication of the degree of malignancy. The invasive type is characterized by slender, poorly demarcated strands of cancer cells with an indefinite basement membrane between them and the copious connective tissue stroma. The noninvasive type is composed of relatively large, rounded clumps of basal cells, well demarcated by an intact basement membrane from the surrounding sparse connective tissue stroma. Clinically the invasive type tends to show the erosion, ulceration and deep invasion which are characteristic of the rodent ulcer type of basal cell epithelioma (illustrated by figs. 3, 5 and 6), while the noninvasive type tends to show the protruding rounded skin-covered mass characteristic of the nodular type of basal cell epithelioma (illustrated by fig. 4). Of course, intergradations between these two types are frequent.

Of the 174 basal cell epitheliomas in this series, 112 lesions were predominantly of the invasive type (64.3 per cent). A considerable portion of the invasive lesions exhibited some degree of keratinization (24.3 per cent as compared with 2.8 per cent for the noninvasive lesions). Three of the basal cell epitheliomas contained pigment, and 5 had an adenoid cystic structure.

With the usual surgical treatments or treatments by irradiation the invasive type of epithelioma has a distinctly less favorable prognosis than has the noninvasive type largely because of the presence of unsuspected deep extensions. However, by virtue of the microscopic control of the chemosurgical method all the invasive as well as the noninvasive neoplasms in this series were successfully treated.

Effect of Site of Cancer on Prognosis.—All the basal cell epitheliomas in this series were successfully treated regardless of the site of origin. The number of lesions which arose in each site is given in table 3.

TABLE 3.—*Distribution According to Site of Origin of Basal Cell Epithelioma*

Site	Number of Lesions
Cheek	65
Temple	31
Forehead	21
Upper lip (skin)	18
Neck	18
Chin	14
Scalp	7
All sites	174

While these data do not indicate any effect of the site on prognosis, it is obvious that advanced epitheliomas over vital structures, such as the brain or the large vessels of the neck, would have poorer prognoses than would similar lesions in other sites.

THERAPEUTIC RESULTS IN CASES OF SQUAMOUS CELL EPITHELIOMA OF THE FACE

A total of 103 squamous cell epitheliomas of the face were chemosurgically treated during the period of seven and one-half years ending Jan. 28, 1944, which date is three years prior to this writing. The cancers were in all stages from early to far advanced, and 27.1 per cent were recurrent after previous treatment elsewhere. Metastases were present in 11.4 per cent of the cases.

End Results After Three Years or More.—The 103 cases of squamous cell epithelioma observed for a period of three years or more included 33 in the indeterminate group and 70 in the determinate group. Successful results were obtained in 84.3 per cent of the cases in the determinate group.

The primary lesion was eradicated in 68 of the 70 cases in the determinate group in the three year period (97.1 per cent). Most of the failures were due to the presence of uncontrolled regional metastases.

End Results After Five Years or More.—There were 50 cases of squamous cell epithelioma observed for five years or more. Of these cases 22 were in the indeterminate group and 28 were in the determinate group. Successful results were obtained in 82.1 per cent of the cases in the determinate group.

Fig. 7.—*A*, squamous cell epitheliomas of groups A, B and C. *B*, healed lesions. The patient is free of cancer after over six years.

Effect of Size of Lesion on Prognosis.—The squamous cell epitheliomas were divided into four groups according to size as measured at the initial clinical examination: A, under 1 cm. in average diameter (fig. 7); B, 1 to 2 cm. (figs. 7 and 8); C, 2 to 3 cm. (fig. 7) and D, over 3 cm. (fig. 9). All of the 52 lesions in groups A, B and C were successfully treated, but of the 18 lesions in group D only 7, or 38.8 per cent, were

cured. Therefore it is concluded that the prognosis is excellent in squamous cell epithelioma of the face, unless the diameter of the lesion exceeds 3 cm.

The complications which accounted for the poorer prognosis associated with lesions in group D were uncontrolled regional lymph node metastasis in 9 cases, excessive involvement of soft tissues and bone of the temporal region in 1 case and excessive involvement of chin, mandible

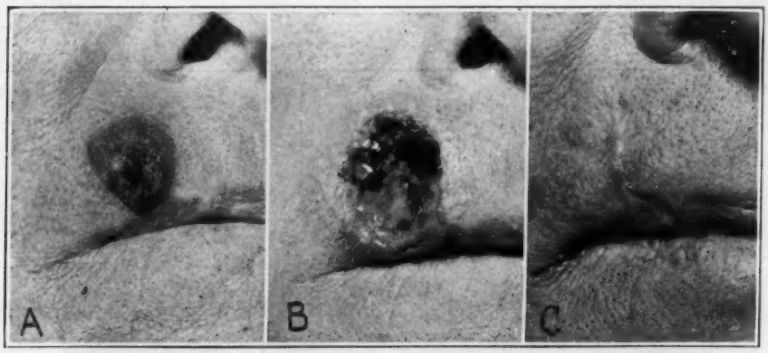

Fig. 8.—*A*, squamous cell epithelioma of group B. *B*, granulation tissue after separation of final layer of fixed tissue. *C*, healed lesion. The patient was free of cancer when he died of other causes after three years.

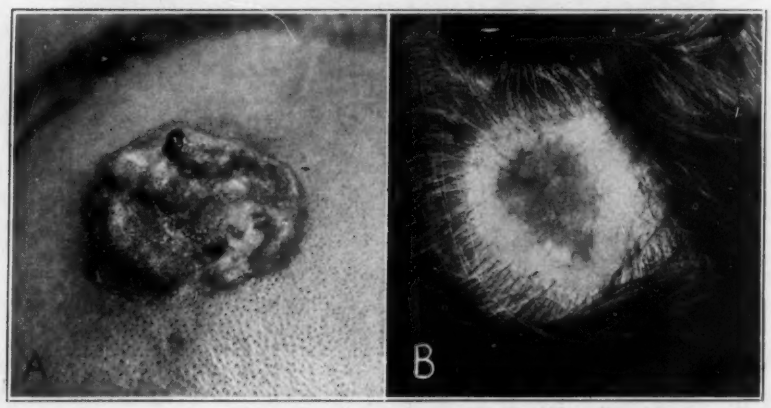

Fig. 9.—*A*, squamous cell epithelioma of group D. The lesion arose in a sebaceous cyst on the scalp. It had recurred after caustic treatments. *B*, healed lesion. The patient is free of cancer after six and one-half years.

and larynx in 1 case. Accordingly, it may be concluded that when a squamous cell epithelioma exceeds 3 cm. in diameter the prognosis becomes poorer because of the increased likelihood of metastasis, the greater chance of the involvement of vital structures and the greater possibility of such extensive involvement of structures of the head and neck that complete removal is impractical.

Effect of Previous Treatment on Prognosis.—Of the 70 squamous cell epitheliomas in the determinate group, 19 (27.1 per cent) had recurred after previous unsuccessful surgical or radiation therapy. The prognosis for previously treated lesions was distinctly poorer than for the previously untreated lesions. Of the 19 previously treated lesions 11 (57.9 per cent) were successfully treated by the chemosurgical method, while of the 51 previously untreated lesions 48 (94.1 per cent) were successfully treated. The poorer prognosis in the group which had previously been treated was not due so much to the effects of the previous treatment per se as it was to the delay which allowed complications such as metastis and excessively widespread local involvement to occur.

Effect of Histologic Grade of Malignancy on Prognosis.—Classification of the 70 squamous cell epitheliomas of the determinate group according to Broder's four grades of malignancy revealed a strong correlation between histologic structure and prognosis (table 4). The greater tendency for early metastasis and for deep invasion into vital

TABLE 4.—*Effect of Histologic Grade of Malignancy of Squamous Cell Epithelioma on Prognosis*

Grade	Number of Lesions	Successful Results	
		Number	Percentage
1	18	17	94.4
2	31	28	90.3
3	19	14	73.7
4	2	0	0

structures associated with the more highly malignant lesions is responsible for the poorer prognosis. However, a highly malignant epithelioma in which these complications have not occurred is just as readily cured by chemosurgical treatment as one of lower malignancy.

Effect of Site of Cancer on Prognosis.—While there was considerable variation in the proportion of successful results in various sites, not much significance can be attached to the results because of the relatively few cases in some of the groups (table 5). All the unsuccessful results were due to uncontrolled metastasis with exception of 1 lesion of the temple with excessive involvement of the soft tissues and bone and 1 lesion on the chin with excessive involvement of the mandible and larynx.

Effect of Metastasis on Prognosis.—By far the most important single adverse influence on prognosis in this series of squamous cell epitheliomas of the face was the presence of metastasis. Thus, while none of the 9 patients with metastasis were cured, 96.7 per cent of the patients without metastasis were successfully treated.

The primary lesion was successfully treated in all the 9 patients for whom results are listed as unsuccessful because of uncontrolled metas-

tasis. Thus, the difficulty in the eradication of metastases was the most common cause of failure. In only 3 cases was an attempt made to dissect out the nodes. In the remaining cases the extent of metastatic spread or the poor general condition of the patients contraindicated any treatment except palliative roentgen ray therapy, which was given in several instances.

THERAPEUTIC RESULTS IN OTHER NEOPLASTIC AND PRENEOPLASTIC LESIONS OF THE FACE

The microscopic control of excision provided by the chemosurgical technic is also useful in the treatment of other neoplastic and preneoplastic lesions of the face.

Fibroma.—Four fibromas, 2 of the neck and 2 of the scalp, were chemosurgically excised with satisfactory results. There has not been any recurrence after periods of from four months to two years.

TABLE 5.—*Effect of Site of Origin of Squamous Cell Epithelioma on Prognosis*

Site	Number of Lesions	Successful Results	
		Number	Percentage
Upper lip (skin)	3	3	100.0
Cheek	33	30	90.9
Neck	10	9	90.0
Forehead	6	5	83.3
Temple	14	10	71.4
Chin	2	1	50.0
Scalp	2	1	50.0
All sites	70	59	84.3

Hemangioma.—Twelve hemangiomas of the face were chemosurgically excised with satisfactory results and without recurrence after periods of observation up to five years. The microscopic control usually is not necessary, because the blood in the vessels turns black on coagulation by the fixative, while the surrounding tissue turns white. Therefore, the extent of the hemangiomatous tissue is easily visualized with the naked eye.

Nevus.—Sixty-four nevi were chemosurgically excised from the face without recurrence or complications after periods of observation up to eight years. The procedure includes a vertical section through the center of the chemosurgically excised specimen. If the nevus cells are observed to extend more deeply, the fixative is reapplied and a horizontal section is made through the bottom of the next excised layer. These precautions are taken to insure elimination of all of the nevus which, if incompletely removed, might lead to melanoma.

Keratoses.—A total of 164 keratoses were removed with the chemicals used in the chemosurgical technic, and not in any instance has cancerous change supervened after periods of observation up to eight years.

Ninety-six of the lesions were senile keratoses, 36 were seborrheic keratoses, 26 were so-called squamous cell papillomas and 6 were cutaneous horns.

The procedure used depends on the clinical appearance. If the keratosis appears "inactive," that is, if it shows little evidence of proliferation in its base, it is often sufficient to cut or scrape off the keratin and cauterize the base with dichloroacetic acid. This procedure is also sufficient for the usual case of seborrheic keratosis.

However, if the keratosis shows evidence of becoming "active," as indicated by proliferation of the epithelium at the base, by induration or ulceration, it is safer to excise chemosurgically a layer for microscopic examination. This procedure eliminates the danger of failing to diagnose and treat adequately an early epithelioma.

COMMENT

The reliability of the chemosurgical method is indicated by the fact that in the determinate groups in the three year period 100 per cent of the 174 basal cell epitheliomas were successfully treated, while 84.3 per cent of the squamous cell epitheliomas were cured.

The best series reported in the literature, not only from the standpoint of excellence of results, but also from the standpoint of statistical validity, is that of Magnussen.[8] He reported the results obtained in the treatment of epithelioma of the face with the advanced radiologic, surgical and electrosurgical technics employed at *Radiumhemmet* in Stockholm, Sweden. From his protocols it was determined that in the three year period successful results were attained in 95.2 per cent of the 169 cases of basal cell epithelioma of the face in the determinate group. For squamous cell epithelioma successful results were attained in 76.2 per cent of 42 cases.

The results of chemosurgical treatment compared favorably with the results of Magnussen. Thus, for the basal cell epithelioma the rate of cure in the present series was 100 per cent as compared with 95.2 per cent in Magnussen's series. This record was attained in spite of a greater proportion of large lesions (32.8 per cent were in groups C and D, as compared with 28.3 per cent in Magnussen's series) and in spite of a greater proportion of recurrent lesions (34.5 per cent as compared with 32.8 per cent in Magnussen's series). Similarly, for squamous cell epithelioma the rate of cure in the present series was 84.3 per cent as compared with 76.2 per cent in Magnussen's series in spite of the greater proportion of large lesions (40 per cent in groups C and D as compared with 27.5 per cent in his series) and in spite of the greater

8. Magnussen, A. H. W.: Skin Cancer: A Clinical Study with Special Reference to Radium Treatment, Acta radiol., 1935, supp. 22, p. 1.

proportion of recurrent lesions (27.1 per cent as compared with 14.3 per cent in Magnussen's series).

The unprecedented reliability of the chemosurgical method is not due to an excessively radical approach since only 1 or 2 mm. of tissue need be removed beyond the level of cancerous invasion. Both the reliability and the conservatism are the results of the systematic microscopic control of excision which is made possible by the chemosurgical technic.

The microscopic control is needed because of the strong tendency for epitheliomas to exhibit irregular and often unsuspected outgrowths from the main cancerous mass. These silent outgrowths are more common and more extensive in advanced and in recurrent epitheliomas, but they are not infrequently observed in early lesions as well.

Another advantage of the chemosurgical method is the practically complete lack of mortality due to the operation. This is an important feature, because many patients with epithelioma are elderly and in poor general health.

A disadvantage of the method is that specialized training and experience are required for the attainment of the best results.

SUMMARY AND CONCLUSIONS

The present series includes 232 basal cell epitheliomas and 103 squamous cell epitheliomas of the face treated by the chemosurgical method and observed for periods of three years or more.

Successful results were attained in 100 per cent of the cases of basal cell epithelioma of the face in the determinate groups in both the three year and five year periods of observation. These results were attained despite the fact that many of the cancers were advanced and over a third had recurred after previous unsuccessful treatment by means of surgical excision, irradiation or caustics.

Successful results were attained in 84.3 per cent of the cases of squamous cell epithelioma in the determinate group in the three year period even though many of the cancers were advanced; 27.1 per cent had recurred after previous treatment and 11.4 per cent had regional metastases. In the five year period of observation successful results were attained in 82.1 per cent of the cases.

The unprecedented reliability of the chemosurgical treatment of cancer of the face is attained by virtue of the systematic microscopic control of excision afforded by the technic. The microscopic control is important because of the frequent occurrence of small caliber, grossly undetectable outgrowths from the main cancerous mass. The reliability is not a result of an excessively radical approach, since only 1 or 2 mm. of tissue beyond the limits of cancerous invasion need be removed.

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ADENOACANTHOMA OF SWEAT GLANDS

Carcinoma of Sweat Glands with Glandular and Epidermal Elements; Report of Four Cases

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THE HISTOLOGIC appearance of carcinomas of the sweat glands has been reviewed in two recent articles written by Loos [1] and by Gates, Warren and Warvi.[2] The number of cases in the literature accepted by these authors as instances of carcinoma of sweat glands is small. Loos, in 1936, enumerated 28 cases and added 1 of his own; Gates, Warren and Warvi, in 1943, enumerated 30 cases and added 6 personally observed cases. Five of the tumors regarded by Loos as carcinomas of sweat glands were not accepted by Gates, Warren and Warvi. The latter authors stated that even among the tumors which they accepted several did not entirely qualify as carcinomas of sweat glands and might have been either adenoid basal cell epitheliomas or hidradenomas.

Carcinomas of the sweat glands do not possess a characteristic appearance. This makes their recognition and their distinction from other cutaneous tumors often difficult. Loos has suggested classification of carcinomas of sweat glands by dividing them into alveolar, tubular, cystic-papillary and solid forms. He pointed out that combinations of these forms were frequent. Although he took cognizance of the fact that "metaplastic cellular changes in the direction of spinocellular, cornifying proliferations" had been described in several cases, he did not group such tumors as a separate form of carcinoma of the sweat glands.

The histologic appearance of carcinomas of sweat glands in 4 patients studied at the Massachusetts General Hospital is herein described. The interesting feature of these tumors is the presence of squamous and keratinized cells in addition to glandular cells.

REVIEW OF THE LITERATURE

In 8 of the 41 cases of carcinoma of sweat glands regarded as such by either Loos or Gates, Warren and Warvi the carcinoma contained

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1. Loos, H. O.: Die Carcinome der Anhangsgebilde der Haut, Arch. f. Dermat. u. Syph. **174**:465, 1936.

2. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591, 1943.

areas of squamous epithelium. None of the 8 tumors showed connections with the epidermis. In 5 of the 8 tumors partial keratinization of the squamous cells was present. It is my belief that several of the 8 tumors were benign tumors of sweat glands rather than carcinomas of sweat glands. A short review of the 8 tumors is given here.

Cornil [3] described a tumor which had been present on the scrotum of a 59 year old patient for six months and which had become ulcerated. The tumor was a squamous cell epithelioma. At the periphery of the lesion Cornil noted the presence of hypertrophic sweat glands with metamorphosis of glandular cells into squamous cells. There were no connections between these sweat glands and the squamous cell epithelioma.

Hufschmitt and Diss [4] observed a patient in whom, at the age of 37, a solitary tumor had appeared on the scalp. After excision, at the age of 57, the tumor recurred and numerous others formed in its vicinity, so that, at the age of 61, three quarters of the scalp was covered with tumors. Some of them were ulcerated, and others were not. Histologic examination revealed that the tumors were composed of sharply outlined epithelial strands which at first sight were suggestive to the authors of basal cell epithelioma. However, most of the cells were connected by intercellular bridges. No development into horn cells was observed. Because of the presence of true glandular lumens in almost every epithelial strand, the authors concluded that the tumors represented carcinoma of the sweat glands.

Grynfeltt [5] reported a solitary small nonulcerated tumor which had been present for five years in the left inguinal region of a woman aged 26. Histologic examination revealed a tumor composed of lobules of various sizes. The lobules contained glandular lumens surrounded by cells of two types. They corresponded to the two types of cells which form the inner and the outer layer of normal sweat ducts. The tumor was composed mainly of cells of the outer layer. Many of them showed intercellular bridges, though less distinctly than the cells of the normal epidermis. There was no evidence of cornification.

The tumors reported by Ruge [6] and Schiffmann [7] were located on the labia majora. Histologically, they were glandular tumors with numerous papillary projections into their lumens. It is my belief that

3. Cornil, V.: Contributions à l'histoire du dévelopment histologique des tumeurs épithéliales, J. de l'anat. et physiol. **2**:476, 1865.

4. Hufschmitt and Diss: Epithélioma sudoripare, Bull. Soc. franç. de dermat. et syph. **36**:503, 1929.

5. Grynfeltt, E.: Tumeur sudorifère de la région inguinale, Bull. Assoc. franç. p. l'étude du cancer **18**:64, 1929.

6. Ruge, H.: Ueber Vulvaaffektionen und ihre gynäkologische Bedeutung (Schweissdrüsenkarzinome), Ztschr. f. Geburtsh. u. Gynäk. **56**:307, 1905.

7. Schiffmann, J.: Schweissdrüsenadenoccancroid der Vulva, Zentralbl. f. Gynäk. **44**:59, 1920.

they were papillary hidradenomas rather than carcinomas. Both tumors showed in a few areas horn pearls surrounded by squamous cells.

Ricker and Schwalb [8] and Dusseldorp [9] each described a tumor located in the right upper eyelid. The 2 tumors were of small size and had been present for six and seven years, respectively. Histologically, they were encapsulated epithelial tumors containing glandular lumens. Both tumors showed areas in which cells with intercellular bridges and horn pearls were present.

In contrast to the aforementioned 7 tumors in which cornification was either absent or present only to a slight degree, the tumor reported by Deichstetter [10] showed considerable cornification. It is the only tumor which resembles the 4 tumors observed at the Massachusetts General Hospital. The patient, aged 65, had had a traumatic ulcer on his left arm for sixteen years. During the last year the ulcer had grown to a size of 8 by 11 cm. The regional lymph nodes were not enlarged. The ulcer was excised. Histologic examination revealed in the corium numerous large "alveoli" filled with large bright flat epithelial cells resembling squamous cells. In some areas within the alveoli the cells were concentrically layered, the innermost layers of epithelium being keratinized. Thus, rather numerous horn pearls were present in the alveoli. In addition, the tumor showed small narrow intertwining strands of epithelial cells. Numerous sweat glands were present beneath the tumor. Some were normal, others showed cystic dilatation of their lumens and still others showed active proliferation of their epithelium with penetration through the membrana propria of the glands. Deichstetter concluded that the origin of the carcinoma was from sweat glands and that the squamous and keratotic cells in the alveoli had developed by metaplasia from glandular cells. He pointed out the analogy to the simultaneous occurrence of adenocarcinoma and squamous cell carcinoma in the corpus uteri and quoted Emanuel's statement [11] that this may be explained by metaplasia of glandular cells into squamous cells rather than by the simultaneous presence of two carcinomas.

REPORT OF CASES

CASE 1.—A 65 year old man was admitted to the Massachusetts General Hospital in January 1942 because of a tumor on his right temple which he had first

8. Ricker, G., and Schwalb, J.: Die Geschwülste der Hautdrüsen, Berlin, S. Karger, 1914, p. 199.

9. Dusseldorp, M.: Adenocarcinoma de glándula de Moll, Rev. de especialid. **4**:999, 1929.

10. Deichstetter, H.: Ueber einen Fall von primärem Schweissdrüsencarcinom, Inaug. Dissert., Munich, C. Wolf & Sohn, 1902.

11. Emanuel, R.: Ueber gleichzeitiges Vorkommen von Drüsenkrebs und Hornkrebs im Uteruskörper, zugleich ein Beitrag zur Histogenese der primären Hornkrebse, Ztschr. f. Geburtsh. u. Gynäk. **46**:434, 1901.

noticed four months previously. Examination revealed a hard, raised, verrucous, centrally ulcerated tumor measuring approximately 1.5 cm. in diameter. The regional lymph nodes were not enlarged. The lesion was excised. When the patient was last seen, in June 1943, there had been no recurrence of the lesion.

Histologic Examination.—The tumor was surrounded by a broad band of granulation tissue. Islands of tumor tissue were present within the granulation tissue (fig. 1).

The epidermis was absent over part of the tumor. In areas where the epidermis was preserved it showed hyperkeratosis and considerable acanthosis. Numerous thick branching protrusions extended from the epidermis into the corium. These epidermal protrusions were composed of squamous cells which in many areas showed concentric arrangement with central cornification. In several areas, cornified

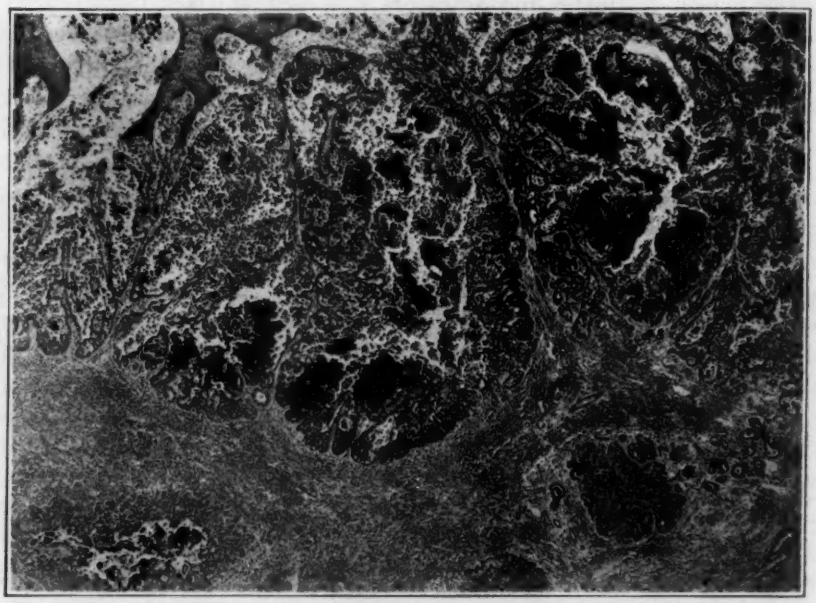

Fig. 1 (case 1).—The tumor contains large alveolar spaces into which papillary projections protrude and which are filled with desquamated cells. In the granulation tissue beneath the alveolar formations three islands of tumor tissue and several atypical sweat glands or ducts are present.

cells filled, either partially or completely, round to oval ductlike lumens (fig. 2) which suggested in their appearance intraepidermal sweat ducts. Many cells were atypical in appearance. A small number of mitotic figures were present. This part of the tumor was suggestive of squamous cell epithelioma.

From some of the epidermal protrusions long thin strands of epithelial cells extended into the corium. These strands usually consisted of only a single row of cells and enclosed large alveolar spaces. At their fundi, the alveolar spaces were lined by several layers of epithelial cells. Some of the alveolar formations lay so close to one another that only a thin layer of connective tissue separated their epithelial linings. Numerous papillary projections protruded from the walls

of the alveolar formations into their lumens. The projections consisted either of clusters of epithelial cells or of long narrow strands of connective tissue lined with usually a single layer of epithelial cells. Most of the epithelial cells lining the aveolar spaces were cubic or cylindric in shape and did not possess intercellular prickles. They appeared to be glandular cells. However, in areas where several layers of epithelial cells were present, the cells of the upper layers had an irregular shape and prickles were noted between them (fig. 3). The lumens contained desquamated epithelial cells. Most of these cells had undergone keratinization. Their cytoplasm had a homogeneous glistening appearance and showed either eosinophilic or, in the most completely keratinized cells, basophilic staining. Some of the cells appeared shrunken, and others were swollen to twice the size of the epithelial cells lining the cysts.

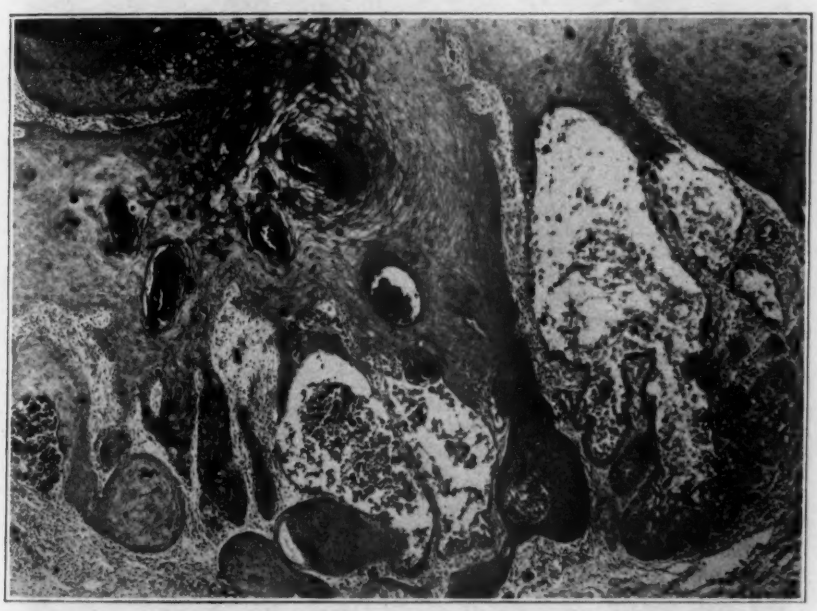

Fig. 2 (case 1).—The epidermis shows atypical proliferations consistent with squamous cell epithelioma. They contain ductlike lumens (sweat ducts) filled partially or entirely with cornified cells. Large alveolar spaces lined by glandular epithelium are connected with the epidermis.

Within the broad band of granulation tissue, scattered islands of epithelial cells were present (figs. 1 and 4). In some islands the epithelial cells lay irregularly, and in others they were in part arranged in strands or around small lumens. A few of the islands contained large central cystic lumens loosely filled with desquamated cells in various stages of keratinization. The majority of the cells composing the islands had the appearance of glandular cells. However, in areas in which the cells were arranged in several layers, some of the cells showed intercellular bridges and thus had the appearance of squamous cells.

Underneath the cysts and between the epithelial islands groups of small tubular glands were present (fig. 1, right lower corner). Some appeared to be

Fig. 3 (case 1).—High magnification of the fundus of an alveolar formation shows the presence of squamous cells and their development into cornified cells.

normal eccrine sweat glands or sweat ducts, and others differed from normal sweat glands by showing larger lumens into which papillary tufts protruded. Some of the lumens contained desquamated cells. The sweat glands with epithelial proliferations approached in appearance the glandular structures belonging to the tumor.

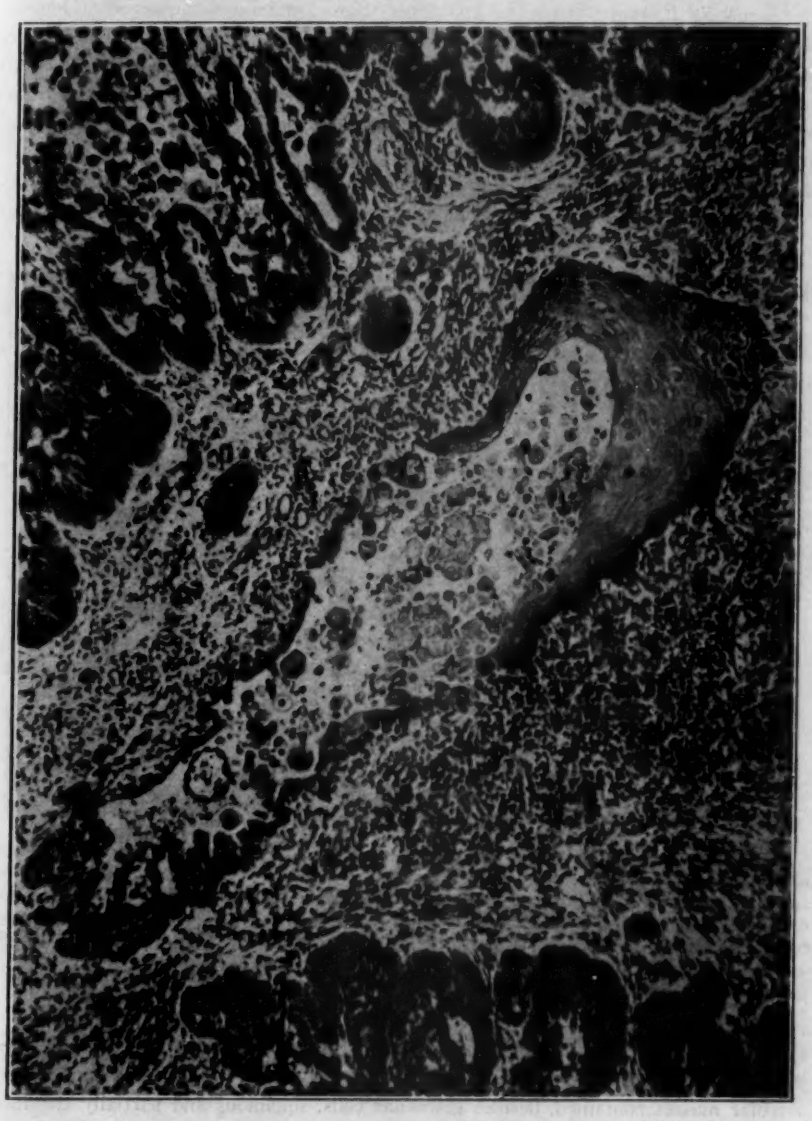

Fig. 4 (case 1).—An island of tumor tissue is shown in which the central cystic lumen is lined at the left by glandular and at the right by squamous cells.

Case 2.—A 79 year old man was seen on several occasions between May 1941 and July 1942 because of senile keratoses on his right ear. They were destroyed by electrodesiccation. In February 1943 the patient returned because of a new

lesion which he had first noticed six months previously. He presented on the anterior aspect of the right ear an indurated, slightly raised tumor which measured 4 by 6 mm. in diameter and had a granular surface covered with a crust. The lesion was excised.

Histologic Examination.—The epidermis showed a moderate degree of hyperkeratosis. In one area the epidermis showed atypical downgrowth consistent with squamous cell carcinoma. Irregular alveolar epithelial masses were connected with this area. Similar alveolar masses without apparent connections with the epidermis were seen elsewhere in the corium (fig. 5). The alveolar masses were predominantly solid, but nearly all contained cystic spaces of irregular outline. Most cells lining the cystic spaces were glandular cells. In areas, however, where the walls of the cysts consisted of several layers the cells nearest

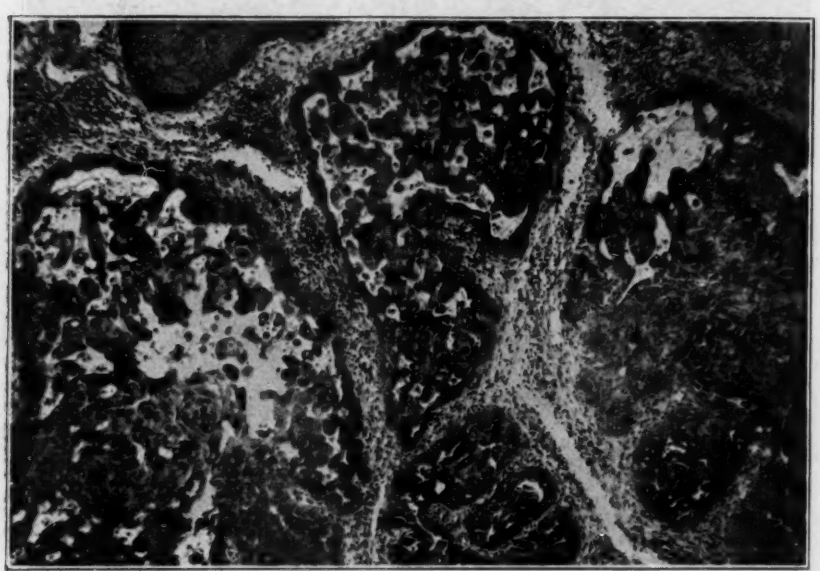

Fig. 5 (case 2).—Alveolar cell masses are located in the corium. The two, located at the left and in the center, are composed mainly of glandular cells and show large lumens containing desquamated, partially cornified cells. The alveolar mass at the right is predominantly solid. Some of its cells are squamous and cornified cells. Several whorls of epithelial cells are present. The cells in the center of the whorls are regarded as glandular, the cells at the periphery as myoepithelial cells. These formations probably represent anaplastic sweat glands.

to the lumen were squamous and partially cornified. The lumens contained desquamated cells showing various degrees of cornification. The solid parts of the alveolar masses contained, besides glandular cells, squamous and partially cornified cells. In addition, whorls of epithelial cells were present, which differed from horn pearls. The cells in the center of the whorls had round or oval nuclei, and those at the periphery had thin elongated nuclei. The central cells resembled glandular cells and the peripheral cells myoepithelial cells. It is possible that these formations represented anaplastic sweat glands. A few sweat ducts with considerable proliferation of their epithelium were seen at the base of the tumor.

CASE 3.—A 77 year old man had been seen intermittently since 1934 because of senile keratoses which developed on various parts of his face. In 1938 a basal cell epithelioma appeared in the nasolabial fold and was treated with radium. In

Fig. 6 (case 3).—A large alveolar space lined by glandular epithelium is shown. There are papillary projections into the lumen. The lumen contains desquamated cells, many of which have the appearance of squamous or keratinized cells.

December 1944 a senile keratosis on the right ear was first noticed. It was electrodesiccated but recurred, and others developed nearby. When seen in

August 1945 the patient presented on the upper free border of the right ear, in addition to several keratoses, a slightly indurated lesion measuring 6 mm. in diameter and covered by a heavy crust. Removal of the crust revealed a granular surface. The lesion, which was movable against the cartilage of the ear, was excised without injury to the cartilage.

Histologic Examination.—The epidermis was absent in the center of the lesion. At both margins of the ulcer the epidermis was hyperplastic, and alveolar formations originated from the epidermis. Other alveolar formations without visible connections with the epidermis were present in the corium. One of the alveolar formations was large, extending through the thickness of the corium, and the others were small. The alveolar formations possessed an epithelial lining which consisted in some areas of a single layer of cylindric cells and in others of several layers (fig. 6). Wherever there were several layers, the upper layers consisted

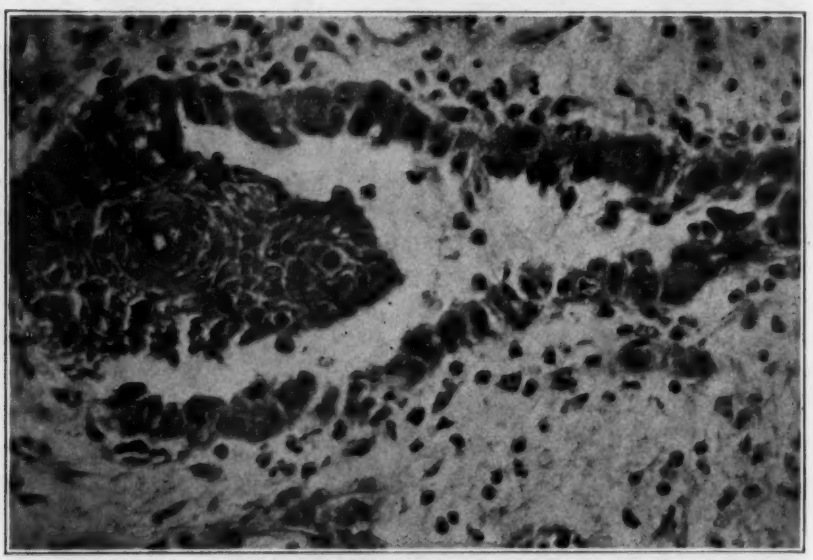

Fig. 7 (case 3).—A large glandular lumen, into which a papillary projection protrudes, is shown. The papillary projection is composed of squamous cells and contains a sweat duct.

of squamous and cornified cells which tended to desquamate into the lumen. There were papillary projections into the lumen lined with either one or several layers of epithelium. One of the smaller alveoli presented an interesting appearance (fig. 7). It was lined by a single layer of cylindric epithelial cells except in one area where there was a papillary protrusion which was composed of squamous cells and had in its center a sweat duct easily recognizable as such by the presence of an eosinophilic cuticle lining the lumen. There were in the corium several groups of sweat glands and ducts, none of which were abnormal.

Case 4.—A 69 year old man was admitted to the hospital in November 1942 because of a lesion on his right ear which he had first noticed nine months previously and which had shown slow but steady growth since. Examination revealed

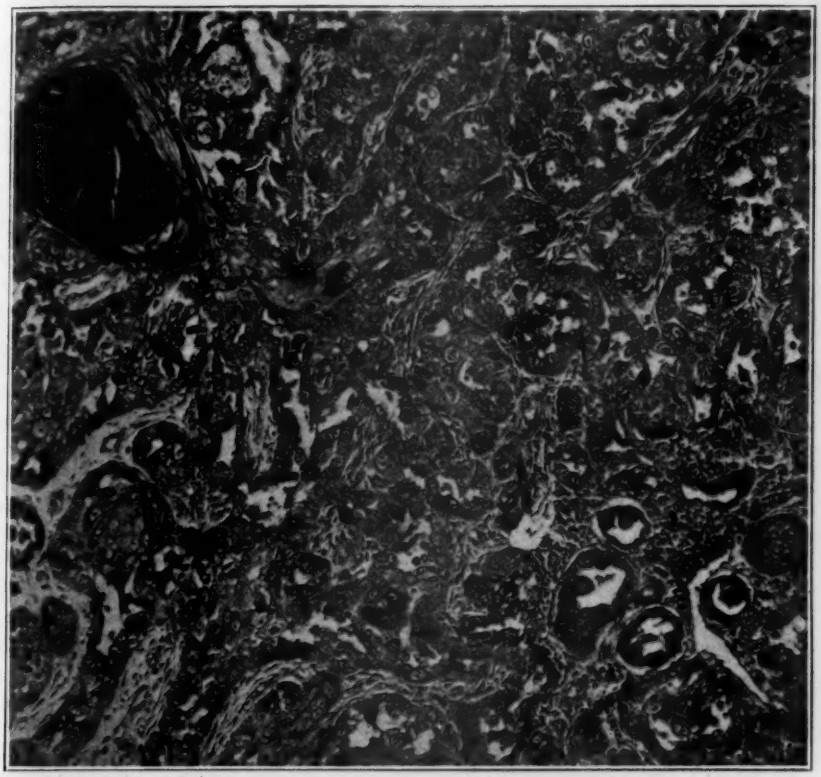

Fig. 8 (case 4).—The tumor is composed of epithelial strands which either are solid or contain a central lumen. Some lumens contain desquamated cornified cells. The centers of some of the solid strands are composed of cornified cells. In the left upper corner, a large area of cornification is seen. In the right lower corner, six sweat ducts are present.

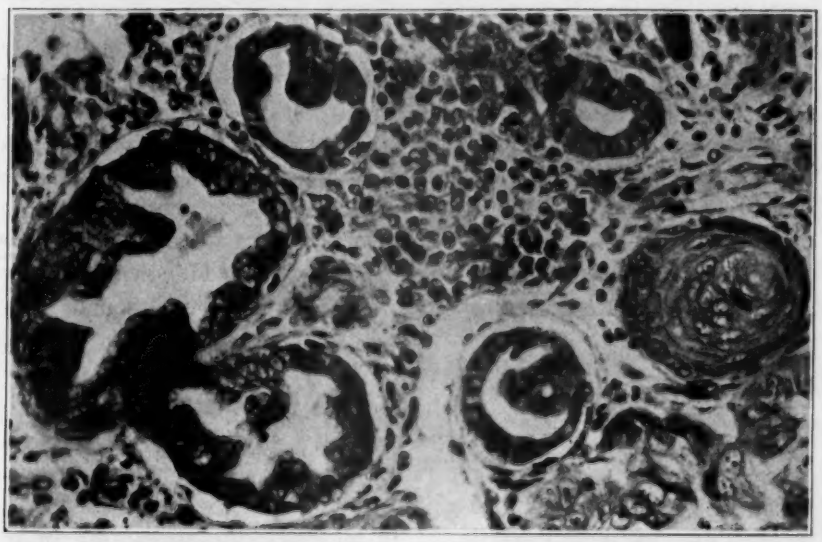

Fig. 9 (case 4).—High magnification of the sweat ducts shown in figure 3. The sweat duct located farthest to the right is of the intraepidermal type (composed of squamous cells), and the others are of the dermal type (composed of glandular cells).

on the upper outer margin of the right ear a raised, round, papillomatous, centrally ulcerated tumor which measured about 1 cm. in diameter and was movable with the skin. There were no palpable lymph nodes. The tumor was excised.

Histologic Examination.—The epidermis was in part absent because of ulceration. In the areas where the epidermis was preserved it was hyperkeratotic and was the site of atypical proliferation consistent with squamous cell epithelioma. From the epidermal processes of the tumor long strands of epithelial cells branched out. The strands formed irregular convolutions which either were solid or possessed lumens (fig. 8). Most lumens were tubular, but a few were alveolar. The alveolar lumens had an irregular outline due to the presence of papillary projections into the lumens. Although most epithelial cells had the appearance of glandular cells, many lumens contained desquamated cells in various stages of keratinization and some of the solid convolutions showed in the center squamous and keratinized cells which occasionally were arranged in the form of horn pearls (fig. 8). The nuclei of the epithelial cells varied considerably in size and shape, and mitotic figures were numerous.

In various parts of the tumor, cross sections of small ducts were present. They were of two types (fig. 9). The ducts of the first type showed glandular epithelium and resembled dermal sweat ducts. Only few ducts of this type had a normal appearance. Most of them showed an irregularly shaped lumen due to the presence of papillary projections into the lumen. The other type of duct showed a slitlike lumen surrounded by an eosinophilic cuticle and by several layers of squamous cells. The presence of an eosinophilic cuticle identified these ducts as sweat ducts. Due to the presence of squamous cells they resembled cross sections of rete pegs containing a sweat duct. They were regarded as intraepidermal sweat ducts. Transitions from both types of sweat ducts to structures belonging to the tumor were observed.

COMMENT

All 4 tumors were observed in men whose ages ranged from 65 to 79. The tumors were all located on the head (3 of them on the ear). In each instance the tumor had been present for only a short time, varying from four to nine months. All 4 tumors were small in size. The smallest measured 6 mm. and the largest 1.5 cm. in diameter. In their clinical appearance the tumors were suggestive of squamous cell epithelioma rather than basal cell epithelioma. Two of the 4 tumors (cases 1 and 4) had a verrucous surface with central ulceration, and 2 (cases 2 and 3) had a granular surface covered with a crust. None of the tumors had caused metastases and none recurred following excision.

From the histologic point of view, the tumors were thought to be carcinomas because of their invasive growth, the atypicality of their epithelial cells with great variation in their size and shape and the presence of mitotic figures. The presence of lumens surrounded by columnar cells in all 4 tumors was suggestive of an origin from tubular glands. Within or close to the tumors eccrine sweat glands and ducts were seen. Some of them had a normal appearance, while others showed proliferation of their epithelium. In all cases, the appearance of the altered sweat glands and ducts approached that of parts of the tumor.

It was, therefore, concluded that the tumors represented adenocarcinomas of eccrine sweat glands.

The 4 tumors were, however, not pure adenocarcinomas. In areas where the lumens were lined by more than one layer of cells, squamous and keratinized cells frequently formed the inner layers, and many lumens contained desquamated keratinized cells. Furthermore, all 4 tumors contained solid areas composed of squamous and keratinized cells which had the appearance of squamous cell epithelioma, and 3 tumors showed atypical proliferations of their epidermis consistent

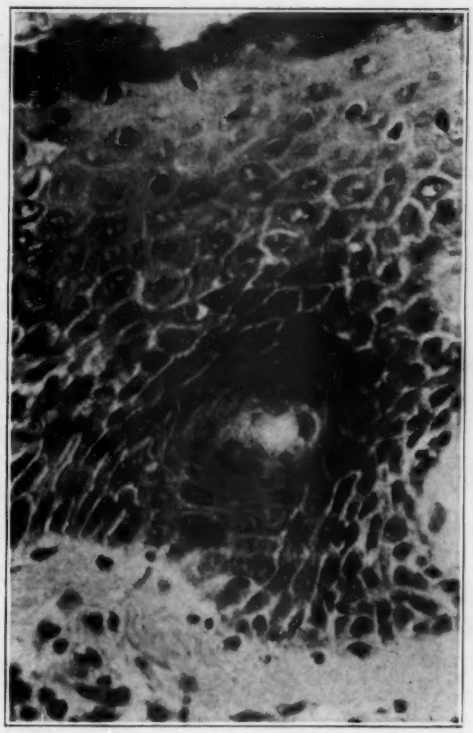

Fig. 10.—A normal sweat duct located in normal epidermis is shown. It is surrounded by squamous cells.

with squamous cell epithelioma. The epidermal proliferations merged with the glandular parts of the tumors without clearly defined border.

Thus, the tumors represented adenocarcinomas of sweat glands with areas of squamous cell epithelioma.

It is not admissible to regard the tumors as combinations of two independent types of carcinoma because the two components were so closely interwoven. Although no adequate explanation of the histogenesis of the tumors can be offered, two theories deserve consideration.

First, these tumors may be adenocarcinomas with metaplasia of glandular into squamous epithelium. The presence of various stages of development of glandular cells into squamous and keratinized cells is in favor of this theory. Or, second, these tumors may represent carcinomas of the epidermal as well as of the dermal parts of sweat ducts. Since inside the epidermis the walls of the sweat ducts are formed by squamous cells and not by glandular cells (fig. 10), it is believed possible that carcinomatous anaplasia affecting the sweat ducts may produce not only an adenocarcinoma but also a squamous cell epithelioma. In other words, the tumors may carry out both potentialities inherent to the tissue from which they originate. The presence of squamous cell epithelioma inside the epidermis in the tumors of cases 1, 2 and 4, the presence in the epidermis of ductlike lumens filled with cornified cells in case 1 and the presence of sweat ducts with walls composed of squamous cells deep in the tumors of cases 3 and 4 are factors in favor of the second theory. Though the second theory appears more plausible, it is possible that the mechanics of both theories combined in the genesis of these tumors.

It is surprising that only one author, namely Deichstetter,[10] has described a tumor of this type, whereas 4 such tumors were observed at one hospital within four years. It is likely that tumors of this type have previously been regarded either as squamous cell epithelioma with degeneration in the center of the tumor masses or as basal cell epithelioma. For instance, Ewing's book on neoplastic diseases [12] contains the photograph of a tumor similar in appearance to the tumors in cases 2 and 3 which was regarded by Ewing as a basal cell epithelioma.

The designation adenoacanthoma of sweat glands is suggested for these tumors. The term adenoacanthoma has been chosen because it is already in use for tumors composed of glandular and squamous elements. Such tumors have been described as occurring mainly in the corpus uteri, but occasionally also in the esophagus and other organs.

SUMMARY

Carcinoma of the sweat glands containing glandular as well as epidermal structures have only rarely been mentioned in the literature and have so far not found recognition as a distinct type of carcinoma of the sweat glands: Four such tumors were observed at the Massachusetts General Hospital.

These tumors show tubular and alveolar lumens lined with one or several layers of epithelium. In areas where the lumens are lined with a single layer of epithelium the epithelial cells have the appearance

12. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 903.

of glandular cells, and in areas with several layers of epithelium squamous and partially keratinized cells usually form the inner layers. The lumens are filled with desquamated cells, many of which are partially or completely keratinized. In addition, there are solid areas composed of squamous and keratinized cells which have the appearance of squamous cell epithelioma. The epidermis may show atypical downward proliferation as in squamous cell epithelioma. Atypical eccrine sweat glands and sweat ducts are present within or at the periphery of these tumors.

The presence of glandular and epidermal elements is probably due to the inherent potentiality of the tissue of origin, the sweat ducts, to differentiate into glandular as well as squamous cells (sweat ducts are formed by squamous cells in the epidermis and by glandular cells in the corium). It is possible that metaplasia of glandular into squamous cells also plays a part.

The term adenoacanthoma of sweat glands is suggested as designation for these tumors.

METASTATIC BASAL CELL EPITHELIOMA

Report of a Case

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NEW YORK

A CAREFUL search of the literature reveals few cases of metastatic basal cell epithelioma. Most of the cases reported as such later proved to be of the basal-squamous type. There are, however, several cases which are generally accepted as metastatic basal cell epitheliomas and a number of others which are thought to be possible cases of metastatic basal cell epithelioma.

In 1931, Niles [1] reported a case of metastatic basal cell epithelioma which later proved to be of the basal-squamous type.[2] A review of the literature in his report included 5 cases of metastatic basal cell epithelioma, 1 each reported by Beadles, Janeway and Körbl (case 61) and 2 reported by Finnerud,[3] and 4 cases of possible, but in his opinion not proved, metastatic basal cell epithelioma reported by D. W. Montgomery, Dubreuilh and Auché, Fordyce and Marassovich.[4]

In 1935, H. Montgomery [5] pointed out that the 2 cases reported by Finnerud had been included in his paper [6] on basal-squamous cell

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Niles, H. D.: Metastasis of a Basal Cell Epithelioma, Am. J. Cancer **15**:2341, 1931.

2. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, American Journal of Cancer, 1937.

3. (*a*) Beadles, C. F.: Rodent Ulcer, Tr. Path. Soc. London **45**:176, 1894. (*b*) Janeway, H. H.: A Contribution to the Knowledge of the Early Stages of Epithelioma of the Skin, Ztschr. f. Krebsforsch. **8**:403, 1910. (*c*) Körbl, H.: Die Röntgenbehandlung der Hautcarcinome speciell des Basalzellenkrebses, sein histologisches Verhalten vor und nach der Betrahlung, Arch. f. klin. Chir. **97**:752, 1912. (*d*) Finnerud, C. W.: Metastatic Basal Cell Carcinoma from the Skin: Report of Two Cases, J. A. M. A. **82**:775 (March 8) 1924.

4. Montgomery, D. W.: Report of a Case of Epithelioma of the Skin of the Face with Unusual Course of Infection of Lymph Nodes, Ann. Surg. **27**:193, 1898. Dubreuilh, W., and Auché, B.: De l'ulcus rodens, Ann. de dermat. et syph. **2**:705, 1901. Fordyce, J. A.: Cancer of the Skin, J. Cutan. Dis. **20**:147, 1900. Marassovich, G.: Beitrag zur Statistik der Carcinome des Gesichtes und der behaarten Kopfhaut, Deutsche Ztschr. f. Chir. **104**:183, 1910.

5. Montgomery, H.: Histogenesis of Basal Cell Epithelioma, Radiology **25**:8, 1935.

(Footnotes continued on next page)

epithelioma in 1928 and stated that there were only 3 cases of metastatic basal cell epithelioma, those of Beadles [8a] and Janeway [8b] and Körbl's case 61.[8c]

A further check of the recent literature has disclosed several possible cases of metastatic basal cell epithelioma. In 1931, Louste, Thibaut, Caillu and Ragu [7] reported a case of basal cell epithelioma of the skin with apparent metastasis to subcutaneous and bony tissue. Their patient first had a lesion on the central part of the forehead, and later a nodule in the pretragal region developed. The histologic diagnosis of the lesion of the forehead was basal cell epithelioma, and the diagnosis of the zygomatic lesion was epidermoid epithelioma, identical with the first lesion. They considered the pretragal lesion a metastasis of the first lesion even though it was not a lymphatic metastasis, and gave the reasons for their conclusions.

Also in 1931, Goodman [8] reported the unusual case of a subcutaneous basal cell epithelioma with nodal metastasis. His patient, S. B., had a nodule under the skin of the right side of the cheek about 2 inches (5 cm.) in front of the ear. The lesion was excised, as were two recurrences. A histologic examination was made of the second recurrence and revealed a basal cell epithelioma. About a year and a half after the second recurrence, the node directly in front of the right ear became enlarged. The node was removed and diagnosed histologically as a basal cell epithelioma (node).

In 1941, De Navasquez [9] reported the case of A. F., who had a basal cell epithelioma on the forehead which was fixed to both the skin and the bone. The lesion was removed, but four years later the patient died of metastases to lungs, spine, ribs, scapulas, pelvis and upper ends of both humeri. Tumor tissue was also observed within a blood vessel of the sternum, indicating that the metastases were blood borne, since there was no evidence of metastasis to the regional lymph node. The metastases all showed the same histologic features of the primary lesion.

Since there are so few cases of metastatic basal cell epithelioma, it was decided to present the only case on record in sixteen years of service at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

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6. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

7. Louste; Thibaut; Caillu, and Ragu: Case of Basal Cell Skin Carcinoma with Apparent Metastasis to Subcutaneous and Bony Tissue, Bull. Soc. franc. de dermat. et syph. **38**:1446, 1931.

8. Goodman, H.: Subcutaneous Basal Cell Epithelioma with Node Metastasis, M. J. & Rec. **134**:271, 1931.

9. De Navasquez, S.: Metastasising Basal Cell Carcinoma, J. Path. & Bact. **53**:437, 1941.

REPORT OF CASE

W. T., a Scottish American housewife aged 39, entered the New York Post-Graduate Skin Clinic Aug. 12, 1935, with a lesion of the scalp near the crown of the head which had developed eight months previously, according to the patient, after a burn from a permanent wave machine. There was no history of cancer or tuberculosis in her family, and the patient's past history was essentially normal. The lesion had always remained about the same size and was not painful, but frequently discharged. A tentative diagnosis of pyodermic ulcer (possibly epithelioma) was made by the examining physician, with the description of a circumscribed matted and crusted purulent area, apparently superimposed on an ulcer. The Wassermann reaction was negative.

Fig. 1.—Primary basal cell epithelioma of the scalp May 4, 1936.

The patient did not return to the clinic until September 4, when she was treated for a pyodermic ulcer. On March 6, 1936, a biopsy of the lesion of the scalp was made. The pathologic diagnosis, made by Dr. David L. Satenstein, was infiltrating basal cell epithelioma. The entire area was destroyed by curettage and electrodesiccation. The patient attended regularly for dressings. On July 15 the first suggestion of a possible recurrence of the lesion was noted. However, the patient did not attend the clinic from Aug. 3, 1936, to June 7, 1937. On June 30, the recurrent nodule was removed and a specimen for biopsy was taken. A pathologic diagnosis of infiltrating basal cell epithelioma was made. The patient came regularly for dressings until Jan. 10, 1938, when two recurrent nodules were discovered and destroyed by electrodesiccation and curettage. The lesion was dressed regularly, and no evidence of activity was noted in the area of the scar, but on March 4 the attending physician located a robin-egg-sized, slightly movable tumor behind the left ear, which the patient said she had had for six months. The

mass had shown no increase in size during the last three months, was not painful and did not discharge. Three days later, on March 7, a specimen for biopsy was taken. A pathologic diagnosis of infiltrating disseminated basal cell epithelioma was made.

On April 8, the patient was referred to the tumor clinic for consultation and treatment. On April 14, Dr. George F. MacFee made a diagnosis of epithelioma of the scalp with metastasis to the left postauricular lymph node. Dr. D. S. D. Jessup examined the biopsy sections which had previously been made in the skin clinic and concurred in the diagnosis of basal cell epithelioma. A week later, Dr. Jessup reported on the biopsy specimen taken by the tumor clinic from the scalp: basal cell epithelioma of the scalp with growth of basal cells in nests extending through the depth of the section.

The patient was admitted to the New York Post-Graduate Hospital April 24 for radical excision with plastic repair and skin graft. At the operation, on April 25, which was performed by Dr. Alexander Zimany with the patient under ether anesthesia and lasted two and one-half hours, excision and plastic reconstruction with a Thiersch graft from the left thigh were accomplished.

Fig. 2.—Metastatic basal cell lesion of the postauricular lymph node.

Recently Dr. Wilbur Sachs reexamined the biopsy sections of March 6, 1936, June 30, 1937, and March 7, 1938, and diagnosed all three as basal cell epithelioma. There was no evidence of the basal-squamous or mixed type, or of the more serious prickle cell or anaplastic epithelioma. He also made the following histologic descriptions.

Biopsy of March 6, 1936.—Extending down from the epidermis to the bottom of the section was a large epithelial mass arranged in lobes, lobules, strands and bands. About the mass was a considerable increase in connective tissue (fibrosis) with a diffuse fibroblastic cell infiltration. In other areas, chiefly at the periphery of the lesion, was a dense cellular infiltration composed chiefly of plasma cells with some small round cells. The epidermis was moderately acanthotic but otherwise showed no important change. At the other end of the section, the epidermis was entirely missing over the underlying mass.

The mass itself was composed of basal cells with large, deeply stained, round and oval nuclei, and a slight amount of cytoplasm, but nowhere could the outlines of the cells be seen. There were no prickles, whorls or pearls. There was no pigment and the palisade layer was missing throughout.

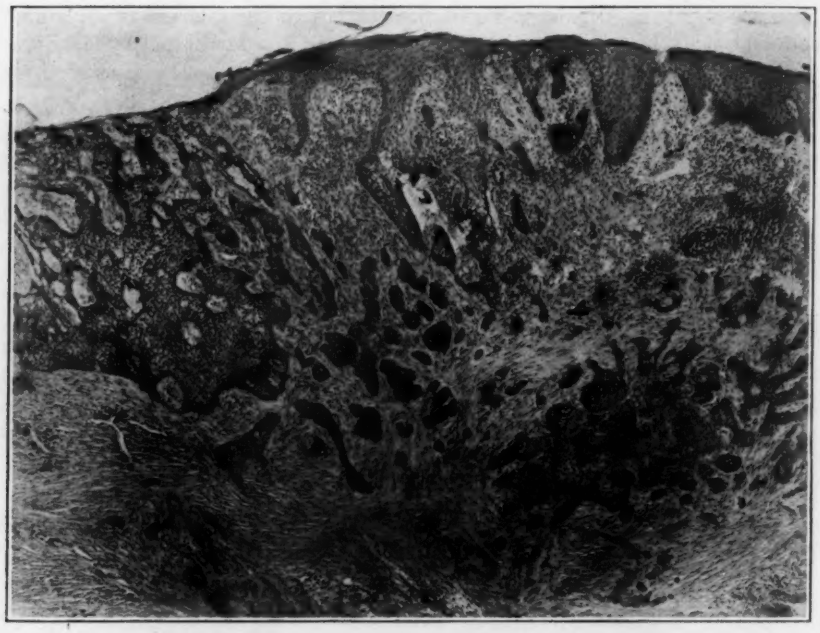

Fig. 3.—Photomicrograph of pathologic section from the lesion of the scalp. (× 49 [approximately].)

Fig. 4.—Photomicrograph of pathologic section from the lesion. (× 49 [approximately].)

In some areas, especially where the fibrosis was greatest, the cells which composed the mass were spindle shaped.

Biopsy of March 7, 1938.—Throughout the section there was an epithelial mass arranged in strands and bands. About the mass was a pronounced increase in connective tissue (fibrosis) with a diffuse fibroblastic cell infiltration. There was no epidermis present.

The mass was composed of basal cells with deeply stained, oval and round nuclei with a slight amount of cytoplasm, but nowhere could the outlines of the cells be seen. There were no prickles, whorls or pearls. There was no pigment and the palisade layer was missing throughout. In some areas the cells were spindle shaped.

The patient was seen at regular intervals until June 12, 1941, which was the date of her last visit. There was no evidence of recurrence at any time during that period, and results were excellent. The patient, however, has failed to return for further examination.

Photographs of the lesions and photomicrographs of the biopsy sections are shown.

COMMENT

Metastasis is the shifting or transplanting of a disease from one organ to another, usually via the lymph channels. The fact that basal cell epitheliomas generally do not metastasize has been noted in numerous papers and textbooks. H. Montgomery,[10] Sohrweide,[11] MacKee and Cipollaro [2] and Andrews [12] have all stated that often the metastatic basal cell epithelioma proves on careful study to have some features of the mixed type or the squamous type in the original or in the secondary lesion and that 15 to 20 per cent of the basal cell epitheliomas which are diagnosed clinically prove on microscopic examination to be basal squamous or squamous cell epithelioma.

MacLeod and Muende [13] considered basal cell epitheliomas as never metastasizing and referred to them as locally malignant.

Cade [14] noted in basal cell epitheliomas that secondary nodules are sometimes seen in the vicinity of the main lesion following the anatomic course of the lymphatics of the skin, indicating that the neoplastic cells directly invade the lymph vessels. However, he pointed out that involvement of the regional lymph node is most exceptional but actually does occur, for in a series of 183 cases of typical basal cell epithelioma in thirteen years, he observed only 1 case.

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10. Montgomery (footnotes 5 and 6).

11. Sohrweide, A. W.: The Basal Cell Epithelioma: A Resumé, M. Times, New York **64**:184, 1936.

12. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, Philadelphia, W. B. Saunders Company, 1939.

13. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, New York, Paul B. Hoeber, Inc., 1940.

14. Cade, S.: Malignant Disease and Its Treatment by Radium, Bristol, John Wright & Sons, Ltd., 1940.

Horsley [15] tried to give an explanation for the lack of metastases in the basal cell epithelioma as compared with the prickle cell type, which metastasizes frequently. He assumed that the basal cells are transported to tissues at a distance from the original lesion but perish because some substance makes their growth in the location impossible. Apparently, in tissues in the immediate neighborhood of the basal cell epithelioma the resistance is weakened or abolished.

Holtzman and Bolker [16] attributed the absence of metastasis in basal cell epithelioma, in spite of the presence of neoplastic tissue in the lymph capillaries, to the inherent cohesion (or continuity) of the protoplasm of these cells.

The case of W. T. apparently is one of the rare instances of a metastatic basal cell epithelioma, for no histologic evidence appears in any of the biopsy material taken that other than basal cell progeny occurred, in either the lesions of the scalp or the lymph node involvement. Sections through the entire lymph node revealed nothing which was reported as mixed, spindle or squamous in types.

It may be that basal cell epitheliomas metastasize as such more frequently, but since such a metastasis is considered unusual it is likely to be overlooked. It is certainly advisable to make a histologic examination of every cancerous lesion and to consider all types as potentially dangerous.

SUMMARY

The case is presented of a patient who had a basal cell epithelioma on the scalp which metastasized to the postauricular lymph node. Since histologic examination of the lesions of the scalp and lymph node revealed basal cell epithelioma, the case is considered to be of metastatic basal cell epithelioma.

105 East Fifty-Third Street.

15. Horsley, J. S.: Basal Cell Carcinoma of the Skin, S. Clin. North America **2**:1247, 1922.

16. Holtzman, I., and Bolker, H.: Basal Cell Epithelioma: A Concept of Its Histogenesis, Am. J. Roentgenol. **47**:463, 1942.

PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

II. The Synergistic or Additive Activity of Penicillin, Oxophenarsine Hydrochloride and Bismuth and Potassium Tartrate

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With the Technical Assistance of ANNA M. RULE

PHILADELPHIA

THAT the simultaneous administration of penicillin by intermittent intramuscular injection over a period of eight days with daily intravenous injections of oxophenarsine hydrochloride in doses of 40 mg. is more effective than penicillin alone in the treatment of early syphilis of adults appears to be well substantiated. The therapeutic effects of the two compounds given simultaneously may be additive, but Eagle, Magnuson and Fleischman [1] have reported that they were apparently synergistic in the treatment of acute syphilitic orchitis of rabbits. For example, these investigators found that when sodium penicillin was injected intramuscularly five times daily at four hour intervals for four days the total minimal curative dose was approximately 8,000 units per kilogram; the concurrent administration of oxophenarsine hydrochloride in subcurative doses of 0.4 mg. per kilogram daily for four days by intravenous injection, however, reduced the total minimal curative dose of penicillin to approximately 1,000 units per kilogram.

As herein reported, these observations have been confirmed. We have also found similar synergistic or additive effects by the simultaneous administration of penicillin and bismuth and potassium tartrate in oil by intramuscular injection in the treatment of acute syphilitic orchitis of rabbits. In the circumstances, it now appears that the optimum therapy for human syphilis may consist of the simultaneous administration of penicillin and oxophenarsine hydrochloride, penicillin and bismuth and potassium tartrate or a combination of all three compounds.

METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of Treponema pallidum. Acute orchitis developed in all,

From the Research Institute of Cutaneous Medicine.

1. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946.

with strongly positive results on dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of seventy days. At the expiration of this time the popliteal lymph nodes of all treated animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

The penicillin employed was a commercial amorphous sodium salt with an assay potency of 544 units per milligram, containing 88 per cent penicillin G, supplied by the Commercial Solvents Corporation (lot no. 45072102).

Aqueous solutions of the compound were freshly prepared as required in sterile isotonic solution of sodium chloride containing 10,000 units per cubic centimeter. Suspensions were prepared in sterile peanut oil and 3 per cent beeswax containing 10,000 units per cubic centimeter and kept at 4 C.

Solutions of oxophenarsine hydrochloride were freshly prepared as required in sterile distilled water. A suspension of the compound was also prepared in sterile peanut oil and 3 per cent beeswax containing 5 mg. per cubic centimeter and kept at room temperature.

Bismuth and potassium tartrate in oil with butacaine sulfate (Abbott Laboratories) was employed. As dispensed, this preparation contained 0.1 Gm. per cubic centimeter; for use it was diluted with sterile peanut oil and 3 per cent beeswax to contain 0.010 Gm. per cubic centimeter.

In some experiments oxophenarsine hydrochloride in peanut oil and beeswax and penicillin in peanut oil and beeswax were mixed immediately before intramuscular injection; the same method was employed in preparing mixtures of penicillin in peanut oil and beeswax and of bismuth and potassium tartrate in oil diluted with peanut oil and beeswax. In this connection we have observed that assays of both mixtures kept at 4 C. every three days over a period of four weeks showed a loss of no more than about 15 per cent of penicillin at the expiration of this period. It would appear, therefore, that the penicillin employed in peanut oil and beeswax remained rather stable in mixtures with oxophenarsine hydrochloride and in mixtures with bismuth and potassium tartrate in peanut oil and beeswax over a period of four weeks at least when kept at a low temperature.

All doses of penicillin were given in terms of units per kilogram of weight by intramuscular injection in the thighs, followed by brief massage. So far as we could judge clinically intramuscular injections of mixtures of penicillin and oxophenarsine hydrochloride and of mixtures of penicillin and bismuth and potassium tartrate in peanut oil and beeswax were well borne, with practically no more local reactions at the sites of injection than produced by penicillin or bismuth and potassium tartrate alone.

RESULTS OBSERVED

Synergistic Activity of Single Doses of Penicillin and Oxophenarsine Hydrochloride.—As previously reported,[2] single intramuscular injections of 100,000 units of penicillin in isotonic solution of sodium chloride per kilogram of weight did not effect the complete or biologic cure of

2. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil–Beeswax by Intramuscular Injection, Arch. Dermat. & Syph. **55**:741 (June) 1947.

acute syphilitic orchitis of rabbits. As shown in table 1, however, single doses of penicillin in isotonic solution of sodium chloride as small as 10,000 units per kilogram by intramuscular injection were completely curative when administered at the same time as 1.0 mg. of oxophenarsine hydrochloride per kilogram by intravenous injection. This single dose of oxophenarsine hydrochloride alone resulted in temporarily negative results on dark field examinations for T. pallidum but was not curative, since the single minimal curative dose of the compound is about 8.0 to 10.0 mg. per kilogram. In the circumstances, the simultaneous injection of one-eighth to one-tenth the minimal single curative dose of oxophenarsine hydrochloride by intravenous injection reduced the single minimal curative dose of penicillin by intramuscular injection from over 100,000 units to probably less than 10,000 units per kilogram of weight.

As previously reported,[2] the single minimal curative dose of penicillin in peanut oil and beeswax was approximately 10,000 units per kilogram of weight in the treatment of acute syphilitic orchitis of rabbits. As shown in table 2, the intramuscular injection of 2,000 units of penicillin along with 2.0 mg. of oxophenarsine hydrochloride in peanut oil and beeswax resulted in biologic cure. This dose of oxophenarsine hydrochloride alone produced temporarily negative results on dark field examinations without biologic cure. The minimal single curative dose of oxophenarsine hydrochloride in peanut oil and beeswax is approximately 20.0 mg. per kilogram. In the circumstances, it appears that the simultaneous intramuscular injection of approximately one-tenth the minimal single dose of oxophenarsine hydrochloride in peanut oil and beeswax reduced the minimal single dose of penicillin in this vehicle from 10,000 units to probably less than 2,000 units per kilogram of weight.

Synergistic Activity of Multiple Doses of Penicillin and Oxophenarsine Hydrochloride.—As previously reported,[2] the minimal curative dose of penicillin in isotonic solution of sodium chloride by intramuscular injection was approximately 1,000 units per kilogram when given twice daily for eight days in succession, totaling 16,000 units. As shown in table 3, however, a dose of 250 units of penicillin per kilogram administered intramuscularly twice daily for eight days in succession, totaling 4,000 units, was completely curative when administered along with 0.2 mg. of oxophenarsine hydrochloride per kilogram by intravenous injection once a day for eight days in succession, totaling 1.6 mg. This dose of oxophenarsine hydrochloride alone produced temporarily negative results on dark field examinations but was not curative. The total minimal curative dose of oxophenarsine hydrochloride by this method of administration was not determined, but in the circumstances the minimal total curative dose of 16,000 units of penicillin in isotonic solution of sodium chloride was reduced to 4,000 units or less per kilo-

TABLE 1.—*The Synergistic Activity of Single Doses of Penicillin in Isotonic Solution of Sodium Chloride by Intramuscular Injection with a Single Dose of Oxophenarsine Hydrochloride by Intravenous Injection*

No.	Penicillin, Units per Kg.	Oxophenarsine Hydrochloride, Mg. per Kg.	Results of Dark Field Examination for T. Pallidum, Days *													Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	10,000	1.0	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
2	10,000	1.0	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	20,000	1.0	2	1	1	—	—	—	—	—	—	—	—	—	—	Negative
4	20,000	1.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	30,000	1.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	30,000	1.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	1.0	4	2	1	—	—	4	4	4	4	4	4	4	4	Positive
8	.....	1.0	4	2	—	—	—	2	4	4	4	4	4	4	4	Positive

* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 2.—*The Synergistic Activity of Single Doses of Penicillin and Oxophenarsine Hydrochloride in Peanut Oil and Beeswax by Intramuscular Injection*

No.	Penicillin, Units per Kg.	Oxophenarsine Hydrochloride, Mg. per Kg.	Results of Dark Field Examination for T. Pallidum, Days *													Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	2,000	2.0	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
2	2,000	2.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	5,000	2.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	5,000	2.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	10,000	2.0	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	10,000	2.0	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	2.0	1	—	—	—	4	4	4	4	4	4	4	4	4	Positive
8	.....	2.0	1	1	—	2	4	4	4	4	4	4	4	4	4	Positive

* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

gram of weight by the simultaneous administration of a total dosage of 1.6 mg. of oxophenarsine hydrochloride by intravenous injection.

As previously reported,[2] the minimal curative dose of penicillin in peanut oil and beeswax was approximately 5,000 units per kilogram when administered intramuscularly once a day for eight days in succession, totaling 40,000 units. As shown in table 4, the intramuscular injection of 1,000 units of penicillin in peanut oil and beeswax once a day for eight days in succession, totaling 8,000 units, was completely curative when oxophenarsine hydrochloride in doses of 0.2 mg. per kilogram was given intravenously at the same time once a day for eight days in succession, totaling 1.6 mg. In the circumstances the simultaneous administration of the oxophenarsine hydrochloride reduced the total minimal curative dose of 40,000 units of penicillin to a total minimal dosage of 8,000 units or less per kilogram.

Synergistic Activity of Penicillin and Bismuth and Potassium Tartrate.—As previously stated, the single minimal curative dose of penicillin in peanut oil and beeswax by intramuscular injection was approximately 10,000 units per kilogram.[2] As shown in table 5, the injection of a single dose of 2,000 units in this vehicle was completely curative when administered along with the intramuscular injection of 0.002 Gm. of bismuth and potassium tartrate per kilogram in peanut oil and beeswax. This dose of bismuth and potassium tartrate alone produced temporarily negative results on dark field examinations but was not curative, since the minimal single curative dose of bismuth and potassium tartrate in oil alone is approximately 0.010 Gm. per kilogram in the treatment of acute syphilitic orchitis of rabbits.[3] In the circumstances the simultaneous intramuscular injection of penicillin in peanut oil and beeswax reduced the single curative dose from 10,000 to 2,000 units or less per kilogram when administered simultaneously with one-fifth the minimal single curative dose of bismuth and potassium tartrate in oil.

As previously stated, the minimal curative dose of penicillin in isotonic solution of sodium chloride by intramuscular injection once a day for eight days in succession was approximately 5,000 units per kilogram per dose, totaling 40,000 units. The minimal curative dose of bismuth and potassium tartrate in oil by intermittent intramuscular injection has not been determined, but, as shown in table 6, the intramuscular injection of 1,000 units of penicillin in isotonic solution of sodium chloride per kilogram once a day for eight days in succession, totaling 8,000 units, was completely curative when bismuth and potassium tartrate

3. Kolmer, J. A.; Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis: I. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**:7 (Jan.) 1939.

TABLE 3.—*Synergistic Activity of Multiple Doses of Penicillin in Isotonic Solution of Sodium Chloride by Intramuscular Injection and Multiple Doses of Oxophenarsine Hydrochloride by Intravenous Injection*

No.	Penicillin *		Oxophenarsine Hydrochloride †		Results of Dark Field Examination for T. Pallidum, Days ‡													Results of Transfer of Lymph Nodes
	Units per Kg.	Total	Mg. per Kg.	Total	1	2	3	7	14	21	28	35	42	49	56	63	70	
1	250	4,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
2	250	4,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	500	8,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
4	500	8,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
5	1,000	16,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	1,000	16,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	.....	0.2	1.6	4	4	4	—	—	2	4	4	4	4	4	4	4	Positive
8	.....	.....	0.2	1.6	4	4	4	—	—	4	4	4	4	4	4	4	4	Positive

* Twice daily for eight days in succession.
† Once daily for eight days in succession.
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 4.—*Synergistic Activity of Multiple Doses of Penicillin in Peanut Oil and Beeswax by Intramuscular Injection and Multiple Doses of Oxophenarsine Hydrochloride by Intravenous Injection*

No.	Penicillin *		Oxophenarsine Hydrochloride †		Results of Dark Field Examination for T. Pallidum, Days ‡													Results of Transfer of Lymph Nodes
	Units per Kg.	Total	Mg. per Kg.	Total	1	2	3	7	14	21	28	35	42	49	56	63	70	
1	1,000	8,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
2	1,000	8,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	5,000	40,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	5,000	40,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	10,000	80,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	10,000	80,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative

* Once daily for eight days in succession.
† Once daily for eight days in succession.
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 5.—*The Synergistic Activity of Single Doses of Penicillin in Peanut Oil and Beeswax and of Bismuth and Potassium Tartrate in Oil by Intramuscular Injection*

No.	Penicillin, Units per Kg.	Bismuth and Potassium Tartrate, Mg. per Kg.	Results of Dark Field Examination for T. Pallidum, Days *												Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	35	42	49	56	63	70	
1	2,000	0.002	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
2	2,000	0.002	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	5,000	0.002	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	5,000	0.002	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	10,000	0.002	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	10,000	0.002	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	0.002	2	1	—	2	4	4	4	4	4	4	4	4	4	Positive
8	.....	0.002	2	1	—	4	4	4	4	4	4	4	4	4	4	Positive

* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 6.—*Synergistic Activity of Multiple Doses of Penicillin in Isotonic Solution of Sodium Chloride and of Bismuth and Potassium Tartrate in Oil by Intramuscular Injection*

No.	Penicillin *		Bismuth and Potassium Tartrate †		Results of Dark Field Examination for T. Pallidum, Days ‡												Results of Transfer of Lymph Nodes
	Units per Kg.	Total	Gm. per Kg.	Total	1	2	3	7	14	21	28	35	42	49	56	63	70	
1	1,000	8,000	0.0005	0.002	2	1	—	—	—	—	—	—	—	—	—	—	—	Negative
2	1,000	8,000	0.0005	0.002	1	1	—	—	—	—	—	—	—	—	—	—	—	Negative
3	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
4	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
5	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
6	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	.....	0.0005	0.002	4	4	4	2	—	—	4	4	4	4	4	4	4	Positive
8	.....	.....	0.0005	0.002	4	4	4	—	—	—	2	4	4	4	4	4	—	Positive

* Once daily for eight days in succession.
† Four doses, given on the second, fourth, sixth and eighth days of treatment.
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

in oil was administered intramuscularly on the second, fourth, sixth and eighth days of treatment in doses of 0.0005 Gm. per kilogram, totaling 0.002 Gm.

SUMMARY

1. The intravenous injection of 1.0 mg. of oxophenarsine hydrochloride per kilogram (one-eighth to one-tenth of the single minimal curative dose) reduced the single minimal curative dose of penicillin by intramuscular injection from more than 100,000 units to probably less than 10,000 units per kilogram in the treatment of acute syphilitic orchitis of rabbits.

2. The intramuscular injection of 2.0 mg. of oxophenarsine hydrochloride per kilogram in peanut oil and beeswax reduced the single minimal curative dose of penicillin in peanut oil and beeswax from approximately 10,000 units to 2,000 units or less per kilogram.

3. The intravenous injection of 0.2 mg. of oxophenarsine hydrochloride per kilogram once a day for eight days in succession (1.6 mg.) reduced the minimal curative dose of approximately 1,000 units of penicillin per kilogram twice daily for eight days in succession by intramuscular injection (totaling 16,000 units) to 250 units or less per kilogram (totaling 4,000 units or less).

4. The intravenous injection of 0.2 mg. of oxophenarsine hydrochloride per kilogram once a day for eight days in succession (1.6 mg.) reduced the minimal curative dose of approximately 5,000 units of penicillin per kilogram once daily for eight days in succession (totaling 40,000 units) to 1,000 units or less per kilogram (totaling 8,000 units or less).

5. The intramuscular injection of 0.002 Gm. of bismuth and potassium tartrate in peanut oil and beeswax per kilogram of weight (one-fifth the single minimal curative dose) reduced the single minimal curative dose of penicillin in peanut oil and beeswax from approximately 10,000 units to probably less than 2,000 units per kilogram.

6. The intramuscular injection of 0.0005 Gm. of bismuth and potassium tartrate in peanut oil and beeswax per kilogram on the second, fourth, sixth and eighth days of treatment (totaling 0.002 Gm.) reduced the minimal curative dose of penicillin in isotonic solution of sodium chloride administered intramuscularly once a day for eight days in succession from approximately 5,000 units (totaling 40,000 units) to 1,000 units or less (totaling 8,000 units or less) per kilogram of weight.

7. Under the conditions, not only oxophenarsine hydrochloride by intravenous and intramuscular injection but bismuth and potassium tartrate in oil by intramuscular injection has shown decided synergistic or additive therapeutic effects in the treatment of acute syphilitic orchitis of rabbits with penicillin.

2101 Pine Street.

PYODERMA GANGRENOSUM IN ULCERATIVE COLITIS

Report of a Case

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ULCERONECROTIC lesions of the skin occurring in association with chronic ulcerative colitis have previously been described by Felsen,[1] Greenbaum,[2] Jones,[3] Brunsting[4] and Cohen[5] under the terms pyoderma gangrenosum and ecthyma gangrenosum. The following case is reported because such lesions are rare and their causation is still controversial.

Felsen described 3 cases in 1941 and reported Escherichia coli, Staphylococcus aureus and nonhemolytic streptococcus in his cases 1, 2 and 3, respectively. He concluded, therefore, that a single bacterial agent is not responsible and expressed the belief that the lesions were probably due to a nutritional disturbance. In reporting 6 cases, Greenbaum also commented on the divergent bacteria observed. His attempts to reproduce lesions by inoculation with a single viable organism failed but were successful when pus was injected into patients in 2 cases and when two organisms were injected simultaneously into patients in 4 cases. He questioned the possibility of a nonbacterial (allergic) factor's being a necessary complement to development of the disease. Jones stated the belief that the lesions were due to deficiency in diet and colonic infection. Cohen reported 1 case in 1936 and pointed out that such lesions are part of a syndrome including recurrence of colitis, hypochromic anemia, hypoproteinemia, fever and foci of infection elsewhere in the body. He considered the cause to be nutritional disturbance with lowered resistance of the skin and secondary bacterial invasion but mentioned elimination of infected teeth as important in curing his patient.

From Lawrence Hospital.

1. Felsen, J.: Multiple Necrotizing Skin Lesions in Ulcerative Colitis, New York State J. Med. **41**:2228 (Nov. 15) 1941.

2. Greenbaum, S.: Inoculation Studies with Viable Bacteria Cultured from Lesions of Pyoderma Gangraenosum, Arch. Dermat. & Syph. **43**:775 (May) 1941.

3. Jones, C.: Peripheral Complications of Ulcerative Colitis, M. Clin. North America **16**:919 (Jan.) 1933.

4. Brunsting, L. A.; Goeckerman, W. H., and O'Leary, P. A.: Pyoderma (Echthyma) Gangrenosum, Arch. Dermat. & Syph. **22**:655 (Oct.) 1930.

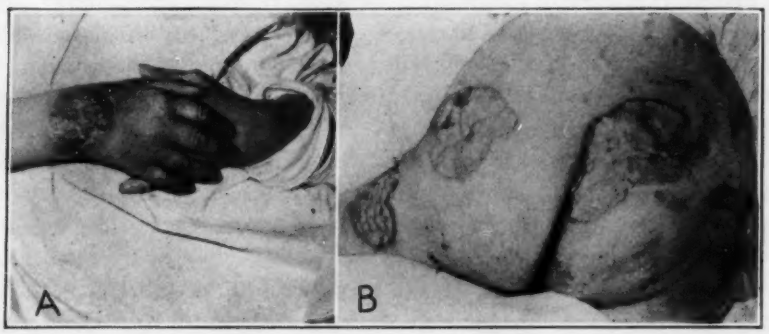
5. Cohen, M. H.: Pyoderma Gangraenosum: A Deficiency Disease Complex, Arch. Dermat. & Syph. **33**: 813 (May) 1936.

REPORT OF A CASE

History.—Mrs. F., a white woman aged 38, was admitted to Lawrence Hospital on Sept. 26, 1944 with the chief complaints of fever, stiffness of the right side of the neck, painful swelling of the right wrist and mild colitis. The present illness began acutely three days before admission.

Her past history revealed that eight years previously she had had "arthritis" in the right wrist and that since then the wrist had been stiff. Three years previously she had been seriously ill and had been hospitalized for several months with ulcerative colitis, diagnosis of which was confirmed by roentgenograms and biopsy. Stool cultures yielded Esch. coli, Escherichia coli hemolytica and some strings of streptococci. No ova or amebas were observed. The patient was told that colitis was secondary to infection of the teeth, but she neglected to have treatment for this condition. Since then she had been fairly well except for mild colitis.

On admission the patient was well nourished and weighed 156 pounds (70.8 Kg.). Her temperature was 102 F., and she was acutely ill. There was gross



A, lesion of the wrist during the fifth week of illness; *B*, lesions of the buttocks during the tenth week of illness.

evidence of infected teeth. The right wrist was red, swollen and stiff. Examination disclosed no other significant abnormalities. The skin was clear on admission, but a few days later a small impetiginous pustule was noted on the right buttock. This later proved to be the first of a series of cutaneous lesions which soon dominated the clinical picture. The pustule opened spontaneously and drained a thin purulent exudate. The lesion continued to enlarge into a rapidly growing ulcer, which at the end of two months was 5 inches (12.7 cm.) in diameter. At the beginning of her third week of hospitalization two small ulcerative lesions developed on the right wrist, and within a week these coalesced to form an ulcer 2 inches (5 cm.) in diameter. During the following week similar lesions developed on the left buttock, both thighs and the entire under surface of both breasts. During the fifth week an erythematous nodule appeared on the right leg. During the next few days this had become a large vesicular lesion 2 inches in diameter. This soon developed into a rapidly growing ulcer, which by the eighth week of hospitalization completely circled the leg from knee to ankle. During these first two months the patient's general condition had become more critical. Temperature of 102 F. had persisted, and the colitis was severe. The patient lost a great deal of weight and was pale.

Description of Lesions.—The lesions began as slightly raised erythematous nodules resembling erythema nodosum. The nodules were several centimeters in diameter. A vesicle filled with cloudy gray or hemorrhagic fluid or a soft area soon developed in the center of each nodule. This sloughed out in a few days, the epidermis remaining for a time as a thin gray translucent film over the crater. The resulting ulcer was phagedenic and grew rapidly. The edge of the ulcer seemed to melt away, so rapidly did the sloughing occur. The base consisted of a soft, boggy, pale and unhealthy-looking granulation tissue covered with thin grayish yellow mucopurulent exudate. The edges of the ulcer were raised and slightly undermined. The dead skin along the edge could be peeled off, and the skin under it had a pearly gray appearance. The skin surrounding the ulcer was indurated and red for about ½ inch (1.27 cm.), and there were small satellite vesicles in this area. The ulcers were irregular in shape, roughly circular and varied in size. The distribution was roughly symmetric. The lesions did not spread to contiguous surfaces, as evidenced by the lesions on the breasts where inability to keep dressings in place meant that the ulcer touched the adjacent thoracic wall without inducing lesions. The lesions were tender. Healing, which coincided with improvement in the patient's general condition, was characterized by epithelization from the edges of the ulcer and from islands of epithelium which appeared in the center of the lesions. Large scars resulted.

Laboratory Data.—The blood count on admission showed 95 per cent hemoglobin and 5,900 white blood cells with 77 per cent polymorphonuclear leukocytes, 92 per cent of which were young forms. A month later the hemoglobin was 65 per cent and the leukocyte count was 10,700 with 46 per cent polymorphonuclear leukocytes, 82 per cent of which were young forms. The urine showed a trace of albumin and many pus cells. The first cultures of the cutaneous lesions showed only a diphtheroid. Cultures of a freshly opened vesicle, which were made to rule out secondary contamination by cutaneous organisms, were negative both aerobically and anaerobically. Cultures for blastomycosis, actinomycosis and sporotrichosis were negative. A smear from a vesicle showed many polymorphonuclear leukocytes and red cells but no organisms or amebas. A biopsy of the margin of one of the ulcers showed a simple ulcerative process in the skin extending down into the fat. The reaction was almost wholly polymorphonuclear in type. The margins of the skin showed the remnants of blebs with loose epithelial cells in the fluid beneath the epidermis. There was no evidence of distinctive granuloma about the ulcer. The subcutaneous tissues near the ulcer were essentially normal. The Wassermann reaction of the blood was negative, and blood cultures were negative both aerobically and anaerobically. A roentgenogram of the teeth showed many root fragments with apical abscesses. A roentgenogram of the chest showed a few fibrotic strands and calcified nodes, suggesting an old infection with tuberculosis. A roentgenogram of the right wrist showed decided increased density of the lateral half of the semilunar bone. The stools were described as mucopurulent and bloody. Stool cultures showed Streptococcus viridans. No amebas or ova were observed.

Treatment and Course.—The patient was treated with vitamins, liver and iron and whole blood transfusions. Penicillin, 20,000 units intramuscularly every three hours, was given for ten days at the end of the first month. There was no improvement in the lesions present, but after this no new ones developed. Fever and colitis continued, and her general condition was critical. All lesions continued to spread at an alarming rate. During the seventh week penicillin therapy was started again, and three abscessed teeth were extracted. Cultures

of the teeth showed Str. viridans and Staphylococcus albus. During the eighth week the lesion on the wrist which had been dressed with plain petrolatum gauze showed evidence of healing, but all other lesions which had been similarly dressed were much worse. Zinc peroxide paste was tried on the lesions without success. At the end of the eighth week wet dressings of tyrothricin were applied for one-half hour followed by continuous dressings of petrolatum gauze. This subsequently proved to be the best method for keeping the lesions clean and the patient comfortable.

The ninth week the patient showed the first indications of improvement. The temperature fell to 100 F. "Kaopectate" (kaolin and pectin) helped to control the diarrhea, and treatment with "sulfasuxidine" begun at the end of this week seemed to clear the pus and blood in the stools. Plasma transfusions were given because the patient had edema of the face and low serum protein with inversion of the albumin-globulin ratio. Cultures of lesions at this time yielded Proteus organisms, Bacillus pyocyaneus, Esch. coli, Staphylococcus aureus and Str. viridans. During the tenth week, two more teeth were extracted, cultures of which yielded Streptococcus hemolyticus, Staph. aureus and Str. viridans. Cutaneous tests were performed using vaccines made from these cultures. Vaccines of the first two organisms gave a reaction of immunity, but during the next two weeks, two small vesicular lesions similar to the beginnings of the large cutaneous lesions slowly developed at the two sites of the tests made with the Streptococcus viridans vaccine. These ultimately healed, leaving small scars. Two more teeth were extracted during the eleventh week. The following week the patient showed definite improvement. The temperature was normal, and the colitis was improved. The lesions of the breasts were healed, and new skin was present in the center and around the edges of all cutaneous lesions. The blood count was improved, showing hemoglobin 70 per cent, white blood cells 9,800 with 72 per cent polymorphonuclear neutrophils, 22 per cent of which were young forms. Improvement continued during the fourth month of hospitalization. Various ointments were tried to hasten healing, but petrolatum gauze seemed most soothing to the patient. When discharged the patient weighed 116 pounds (52.6 Kg.), a loss of 40 pounds (18.1 Kg.) since admission. Since discharge she has been well and has regained normal weight.

SUMMARY

A case of necrotic ulceration of the skin associated with recurrence of ulcerative colitis, bone marrow depression, hypoproteinemia and fever is described. Healing of the cutaneous lesions coincided with the general improvement which seemed to follow removal of focal dental infection. Cutaneous tests with vaccine made from Streptococcus viridans cultured from the teeth caused small vesicular lesions which resembled the first stage of large cutaneous lesions.

CONCLUSION

Ulceronecrotic lesions of the skin (pyoderma gangrenosum), and possibly the ulcerative colitis with which such lesions are associated, may be manifestations of an allergic reaction to bacterial infection elsewhere in the body, in this case dental abscesses.

26 Pondfield Road West.

REITER'S DISEASE

A Comparison with Keratosis Blennorrhagica and with Psoriasis Arthropathica

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ALTHOUGH Reiter[1] originally described the syndrome bearing his name in 1916, the first case in the English literature was not reported until 1928.[2] However, the disease was not fully accepted in this country until after the report of Bauer and Engelman in 1942.[3] Since 1944 an increasing number of papers on this subject have been presented in the domestic literature. In view of the increasing interest in this disease, a comparison with keratosis blennorrhagica and with psoriasis arthropathica is indicated.

Observations in 75 cases of keratosis blennorrhagica and in 33 cases of psoriasis arthropathica were compared in 1939.[4] This study failed to demonstrate more than a superficial resemblance between the two diseases. Despite the overwhelming evidence that keratosis blennorrhagica and psoriasis arthropathica are distinct entities admitting accurate differentiation, the conviction persisted that some cases of keratosis were not caused by infection with gonococci. As evidenced by the correspondence received after the publication of the aforementioned article,[4] this belief was maintained by many dermatologists. The term "banal keratosis" seemed adequate for instances of keratosis-blennorrhagica-like eruptions not due to gonorrheal infection. However, the increasing recognition of Reiter's disease as an entity forced its consideration in diagnosis of cases falling into this group. Briefly, Reiter's disease consists of urethritis, conjunctivitis and arthritis of unknown cause. Occasionally, cutaneous lesions occur, but in most instances there are no dermatologic manifestations. The more important eruptions have been described as balanitis circinata and, less frequently, as keratosis-blennorrhagica-like.

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1. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

2. Frühwald, R.: So-Called Spirochaetosis Arthritica (Reiter, 1916), Urol. & Cutan. Rev. **32**:7 (Jan.) 1928.

3. Bauer, W., and Engelman, E. P.: A Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**: 307, 1942.

4. Epstein, E.: Differential Diagnosis of Keratosis Blennorrhagica and Psoriasis Arthropathica, Arch. Dermat. & Syph. **40**:547 (Oct.) 1939.

Lever and Crawford [5] stated that only cases including all three of the basic manifestations should be included in this classification. This attitude is justified until a causative organism or a pathognomonic test for Reiter's disease is discovered. However, Hollander and his co-workers [6] included cases of "atypical Reiter's disease" in which only nonspecific urethritis and arthritis were present without conjunctivitis. Perhaps cases could be included in which only the typical arthritis and conjunctivitis are noted. The case reported here is an example of arthritis, conjunctivitis and a keratosis-blennorrhagica-like eruption. This case obviously belongs in the group of diseases under consideration. Although there was no urethritis present and there was a history of an unproved gonococcic infection ten years previously, it is felt that the complete picture adequately conforms to the clinical conception of Reiter's disease.

REPORT OF A CASE

E. D., a 35 year old white man, a taxicab driver, was first seen on May 28, 1945. He stated that he had been discharged from the Army in 1942 because of arthritis. However, the history of repeated pains in the joints was too vague to be of significance. In 1935 he had suffered an attack of purulent urethritis that was presumably due to gonorrhea. This had cleared promptly and had not recurred. There was no history of previous ocular symptoms. He had dropped a heavy weight on his right big toe a year previously, and six months later an operation had been performed to remove a sequestrum.

The patient stated that about the middle of May he had noted an eruption on his scalp which soon spread to his feet and to other parts of his body. There was some febrile reaction. About two days before examination his right big toe became painful and swollen. At the same time there developed redness of the conjunctivas associated with photophobia. There was no urethral discharge during the time the patient was under observation.

On examination the right big toe was edematous, erythematous and semifluctuant. The patient appeared to be ill. His temperature was 103.2 F. by mouth. Both conjunctivas were moderately injected. His entire scalp was involved in a sharply demarcated erythematous crusted eruption. There were a number of small hyperkeratotic pustules with surrounding inflammatory areolas on the elbows, knees, ankles and soles. In addition there were a number of scattered erythematous macules with silvery scaling.

Sulfadiazine in doses of 8 Gm. daily was administered by mouth. Supportive measures were also instituted. The patient was apparently improving for a few days, but on June 4 he experienced an elevation of temperature, polyarthritis affecting mainly the knees and the ankles and an extension of the eruption. The possibility that this exacerbation represented a reaction to sulfadiazine was considered but was ruled out by subsequent developments.

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5. Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389 (June) 1944.

6. Hollander, J. L.; Fogarty, C. W.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome, J. A. M. A. **129**:593 (Oct. 27) 1945.

The patient was hospitalized on June 5 and spent four months in the hospital.

Laboratory Findings.—Routine studies were not remarkable. The blood count repeatedly showed a leukocyte count of 12,000 to 16,000 white blood cells with 70 per cent to 80 per cent polymorphonuclear leukocytes. Urinalyses revealed no abnormalities. Kolmer and Kahn tests of the blood elicited negative reactions. The spinal fluid on examination was also normal.

A smear of prostatic fluid obtained by massage revealed some pus but no specific organisms. The albumin: globulin ratio was consistently reversed, and at times the total was as low as 3.5 mg. per hundred cubic centimeters of blood. Tests of hepatic function revealed no abnormalities. Reactions to intradermal Frei and brucellin tests were negative. Repeated blood cultures failed to result in the growth of any organisms.

Histologic examination of material taken from lesions on the soles showed changes consistent with a diagnosis of keratosis blennorrhagica, i. e., parakeratosis, hyperkeratosis, thickening of the stratum granulosum, acanthosis, elongation of the interpapillary plugs and a superficial inflammatory infiltrate. The latter was basically lymphocytic.

Course and Treatment.—Penicillin administered intramuscularly in doses of 25,000 units every three hours for ten days, a total of 2,000,000 units, did not affect the disease. Salicylates were also ineffective. Two intravenous injections of oxophenarsine hydrochloride failed to alter the course. Bed rest, supportive therapy and physical therapy (heat and massage) gave some relief.

Only two things seemed to be beneficial. Repeated transfusions not only increased his strength and his blood proteins but apparently benefited the eruption and the arthropathy. The patient also received one fever treatment with a modified "blanket method." He was uncooperative, and a temperature between 103 and 104 F. by axilla was maintained for only four hours. However, on the following day a definite improvement occurred in the cutaneous manifestations, and the motion of the affected joints was increased. There was also a decrease in the pain and in the swelling. Unfortunately the patient refused further hyperpyrexial treatment.

The course of the patient was basically downhill with comparative remissions followed by acute exacerbations. The cutaneous manifestations almost disappeared on two occasions prior to the final recovery. The elevated temperature continued for over two months, often reaching heights in excess of 103 F. by mouth. The elevations in the afternoon were often accompanied by chills suggesting septicemia. He lost 60 pounds (27 Kg.) during his hospitalization. The joint involvement spread from articulation to articulation including the temporomandibular articulations and those of the elbows, wrists, hips, hands, knees and ankles. The involved joints were red, hot and tender. Motion was limited by the pain and swelling. No ankylosis developed, although the progress of the disease made me constantly fear the imminence of such a development.

The cutaneous lesions started as small pustules with inflammatory areolas. These occurred in crops. They were most evident on the legs and on the feet but occurred over all of the involved joints. The tendency of keratoses to develop over affected articulations was great. The mouth was also occasionally involved concurrently with a crop of new lesions on the skin, but these lesions would persist for only a few days. The primary pustules would soon undergo hyperkeratotic changes with the eventual development of typical pyramidal waxy

adherent crusts of keratosis blennorrhagica. The individual lesions spontaneously cleared in three to six weeks, but new lesions continued to appear. The eruption was unaffected by local applications, elastic adhesive bandages or large doses of vitamin A. The original eruption on the scalp disappeared spontaneously and did not recur. The conjunctivitis recurred on several occasions.

After the treatment with fever, the patient, who had been apparently moribund, started to improve. The transfusions were continued. Within two weeks the patient was up in a wheel chair and was gaining weight. Except for some residual stiffness in his hips and knees the patient was clinically well a month later. He was able to walk satisfactorily with a cane and was discharged from the hospital. There has been no further observation of this patient.

NATURE OF REITER'S DISEASE

The basic problem concerns the nature of Reiter's disease. Reiter [1] in 1916 described the occurrence of the triad of urethritis, conjunctivitis and arthritis in a single case. He isolated from the blood of his patient a spirochete which he called Spirochaeta forans; he named the disease spirochetosis arthritica. However, later investigators were unable to confirm this observation. The usual spirocheticides have been ineffective in the treatment of this disease. Neither have other suggested causative factors been confirmed. However, most investigators agree that the disease is due probably to an infectious agent.

Therefore, at the present time, Reiter's disease must be considered as a clinical entity. If one can judge from the reported cases, the initial manifestation is usually urethritis, although conjunctivitis may be the first symptom. Both of these manifestations subside in a short time, i. e., days to weeks. The arthritis is most apt to develop in the knees, the ankles and the feet. This persists from two to five months and then clears spontaneously with few or no sequelae. Diarrhea and moderate fever are often noted. The disease may recur in all three basic systems, i. e., skeletal, ocular and urologic, in one or in two of them. Rosenblum [7] mentioned the case of a patient who had recurrent conjunctivitis with later development of the entire triad. Therefore it seems reasonable to suppose that the disease does not necessarily affect the eyes, the urethra and the joints in all cases. Abortive examples may be present either preceding the development of the entire syndrome or as a manifestation of a recurrence.

Usually cutaneous manifestations are absent. Nonspecific eruptions such as simple erythemas, urticaria, erythema nodosum and erythema multiforme may occur but are not of diagnostic significance. On the other hand, those eruptions described as balanitis circinata and as keratosis blennorrhagica hold interest for the dermatologist.

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7. Rosenblum, H. H.: So-Called Reiter's Disease, U. S. Nav. M. Bull. **44**:375 (Feb.) 1945.

Therapy (including administration of penicillin, sulfonamide compounds, arsphenamine, salicylates and colchicine) has been ineffective in modifying the course of the disease. It is suggested that fever therapy may prove of value in combating this disease. In the case reported here even one inadequate treatment resulted in immediate improvement in all of the manifestations. Recovery followed in an apparently moribund patient, and the improvement dated from that treatment. However, it is agreed that Reiter's disease is apparently a self-limited process, and the possibility of coincidental spontaneous recovery cannot be denied.

Differential Diagnosis of Reiter's Disease, Keratosis Blennorrhagica and Psoriasis Arthropathica

	Reiter's Disease	Keratosis Blennorrhagica	Psoriasis Arthropathica
Basic condition.....	Urethritis, arthritis, conjunctivitis	Gonorrhea, arthritis, eruption	Psoriasis, arthritis
Sex.....	Male	Male	Both
Age.....	18 to 40	20 to 50	Any
Familial incidence.....	None	None	Occasionally
Initial manifestation..	Usually arthritis but may be any	Urethritis, arthritis	Eruption
Cutaneous lesions.....	Hyperkeratotic pustules, nonspecific eruptions	Hyperkeratotic pustules	Silvery scaling, pinpoint hemorrhages, etc.
Location of eruption..	Localized especially on hands, feet, penis	Localized especially on hands, feet, penis	Generalized after starting on knees, elbows, scalp, etc.
Pustules.....	Usually present in typical cases	Probably always present	Occasionally present (18.2%)
Arthritis.....	Usually knees and ankles with or without involvement of other joints	Usually knees and ankles with or without involvement of other joints	Usually starts on hands and later spreads to other joints
Ankylosis.....	None	Often	Often

The disease is probably not rare, especially in military installations. After all, Hollander and his co-workers [6] reported 25 cases, Rosenblum [7] 10 cases and Bauer and Engelman [8] 6 cases. A large number of cases are never recognized and/or reported. This single report of a case is presented merely as a text for the comparison of the dermatologic manifestations of Reiter's disease with keratosis blennorrhagica and with psoriasis arthropathica.

COMMENT

The table compares Reiter's disease with keratosis blennorrhagica and with psoriasis arthropathica. The information regarding the latter two diseases is reprinted from a previous article.[4] On the whole, Reiter's disease with keratoses is clinically indistinguishable from keratosis blennorrhagica. However, Reiter's disease is not primarily a dermatologic entity, and keratotic cutaneous lesions occur in only a

small percentage of cases, even as keratotic lesions occur in only a small portion of the cases of gonorrhea or of gonorrheal arthritis. When these characteristic lesions accompany Reiter's triad, the differentiation must be based on laboratory studies and on the course of the disease. One feature of importance is that Reiter's disease does not lead to permanent changes in the joints, while ankylosis commonly supervenes in gonorrhea. However, this is not helpful in the acute phase.

The differentiation of Reiter's disease from psoriasis arthropathica is usually simple as evidenced by the tabulated data. The most important differentiating features are sex, initial manifestation, location of the eruption and type of arthritis. It is not within the scope of this paper to discuss this phase, and so the reader is referred to the previous paper for further details. The case presented offered difficulties in diagnosis because the original lesions resembled those in psoriasis but became hyperkeratotic pustules after the development of the arthritis.

Therefore, the concept of Reiter's disease adequately explains the long recognized fact that "keratosis blennorrhagica without blennorrhagica" does occur. However, it exists only in a specific form, and this term cannot be adopted for all pustular and hyperkeratotic lesions accompanying arthropathies not due to gonorrhea.

SUMMARY

Reiter's disease is compared with keratosis blennorrhagica and with psoriasis arthropathica. The former seldom presents a picture suggesting keratosis blennorrhagica, but when it does the differentiation must be based on laboratory observations and on the course of the disease.

An atypical case of Reiter's disease, apparently favorably affected by fever therapy and by transfusions but not by administration of penicillin and sulfonamide compounds, is presented.

1904 Franklin Street.

CORRELATION OF BOILING RANGES OF SOME PETROLEUM SOLVENTS WITH IRRITANT ACTION ON SKIN

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AND
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PHYSICIANS seeing patients with dermatitis appearing after contact with petroleum products are handicapped in obtaining information regarding the physical and chemical properties of these products. The wide use of nondescriptive brands and trade names and the heterogeneous nature of petroleum products make it difficult to evaluate their role in causing dermatitis. This was apparent in our studies of patients exposed to a class of petroleum derivatives often referred to as mineral seal oils.

Our purpose is to facilitate judgment of the role of petroleum products in causing dermatitis by classifying such products commonly encountered by industrial physicians and to indicate the identifying properties of the various classes.

CLASSIFICATION OF PETROLEUM PRODUCTS

Petroleum is composed of an intimate mixture of thousands of hydrocarbon compounds, with paraffins (C_nH_{2n+2}) and cycloparaffins or naphthenes (C_nH_{2n}) predominating and oleofins, acetylenes, aromatics and other cyclic hydrocarbons present in lesser amounts. Sulfur, oxygen and nitrogen derivatives of the hydrocarbons are present as impurities. The primary separation of petroleum into commercial products is accomplished by means of distillation, each fraction containing the major portion of all compounds having boiling points within the distillation range of the fraction. Therefore the most convenient and reliable means of identification and classification of petroleum products is by their boiling ranges. A simple classification is as follows:

Class I.—Class I consists of distillate products with boiling ranges below 450 F. This group includes materials commonly called naphthas, solvents, gasolines, dry cleaning fluids, paint thinners, Stoddard solvent, lacquer diluents, mineral spirits and petroleum ether.

Mr. Brill is with the Atlantic Refining Company.

Read at the Section on Dermatology and Syphilology at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 5, 1946.

Class II.—Class II consists of distillate products with boiling ranges between 350 and 600 F. These include kerosene, long time burning oil, mineral seal oil, 300 oil, absorbent oil, engine distillate, oils used for insecticide bases, gas oils and no. 1 and no. 2 furnace oils.

Class III.—Class III consists of distillate products with boiling ranges above 600 F. These include light lubricating oils, spindle oils, neutral oils, transformer oils, machine oils and cutting oils.

In chart I are shown graphically the boiling range characteristics of typical petroleum products of a major oil company on the eastern seaboard, and the distillation and other test data are shown in table 1.

Other physical properties of petroleum oils are commonly reported to aid in identification and to indicate the degree of refinement. Among

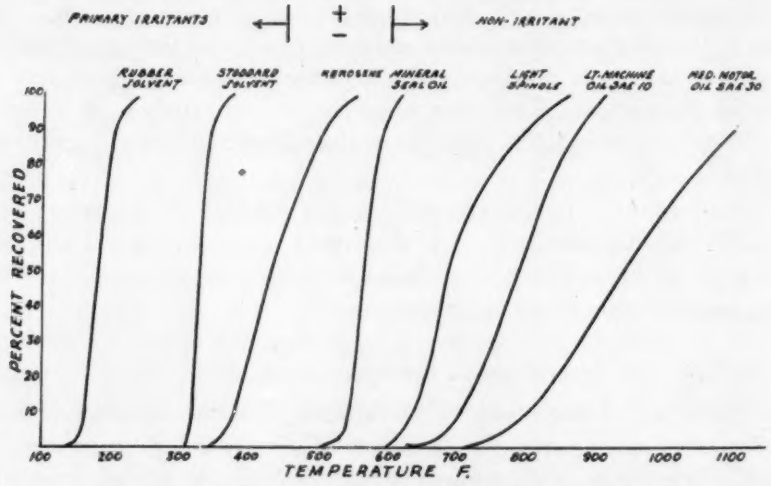

Chart 1.—Boiling ranges of typical petroleum products.

the commonest are specific gravity (A.P.I. [American Petroleum Institute] gravity is used in the petroleum industry), color, flash point, pour point and viscosity. The experienced petroleum technologist can guess as to the origin of the crude oil and the predominant hydrocarbon series present from an inspection including these characteristics. Determination of chemical make-up (hydrocarbon analysis) is a more involved and expensive procedure but would be required if a knowledge of the proportions of the constituent hydrocarbon series is desired.

For example, if two solvents have roughly identical boiling ranges, the one with the higher A.P.I. gravity (lower specific gravity) would be the more paraffinic. Other methods are in common use to supplement this simple criterion, such as aniline point, refractive index, ring number (for kerosene), viscosity-gravity constant and viscosity index. It is sufficient for the purpose of this discussion merely to mention these additional criteria.

Unfortunately, no single characteristic is sufficient to identify a petroleum product, since many commercial preparations are blends of more than one product. Furthermore, it is common practice to introduce additive agents, inhibitors, soaps, fatty oils and other nonpetroleum materials to petroleum products to impart special properties which are not inherent in petroleum itself. Most present day gasolines contain tetraethyl lead, bromine compounds and dyes. Cutting oils often contain sulfur, chlorine derivatives and/or animal oils. Finally, products of similar characteristics are given different names by different manufacturers, and products sold under a common name by different manufacturers often differ appreciably in their properties.

TABLE 1.—*Physical Properties of Typical Petroleum Products*

	Rubber Solvent	Stoddard Solvent	Kerosene	Mineral Seal Oil	Light Spindle Oil	Light Machine Oil, S. A. E.* 10	Medium Motor Oil, S. A. E.* 20
Specific gravity at 60 F...	0.6506	0.7857	0.8063	0.8333	0.8762	0.8956	0.8927
A. P. I. gravity at 60 F...	68.0	48.5	44.0	38.3	30.0	26.5	27.0
Color, Saybolt.....	+30	+30	+20	+18	2 N. P. A.†	2 N. P. A.†	4 N. P. A.†
Flash point, F.....	—20	105	140	275	335	380	430
Kinematic viscosity, centistokes	0.54 at 77 F.	1.08 at 77 F.	1.55 at 100 F.	4.20 at 100 F.	11.75 at 100 F.	33.2 at 100 F.	123.0 at 100 F.
Pour point, F.	—75	—60	—40	20	25	25	0
Distillation (A. S. T. M.)					‡	‡	‡
Initial boiling point, F.	140	308	345	506	600	627	713
End point, F.....	226	372	550	607	840	912	...
5% recovered at, F.....	159	314	369	537	625	687	778
10% recovered at, F.....	161	316	378	544	640	704	805
20% recovered at, F.....	165	318	392	551	650	730	835
30% recovered at, F.....	170	320	403	556	665	752	873
40% recovered at, F.....	175	322	416	559	675	768—	910
50% recovered at, F.....	180	325	431	563	687	788	940
60% recovered at, F.....	184	328	449	568	700	808	970
70% recovered at, F.....	189	331	464	574	720	820	1,010
80% recovered at, F.....	195	335	481	580	755	845	1,047
90% recovered at, F.....	203	343	504	590	800	865	...
95% recovered at, F.....	209	351	521	605	830	893	...

* Society of Automotive Engineers.
† N. P. A. indicates National Petroleum Association.
‡ Converted from vacuum distillation at 10 mm.

Therefore, in any approach to a problem involving a petroleum product it is essential that the manufacturer be requested to supply detailed information as to the physical characteristics of the product and the presence of any nonpetroleum constituents. In general, such information can be divulged qualitatively without involving so-called trade secrets, and any reputable petroleum refiner would comply with such a request when the purpose of the inquiry is made known by the physician.

Since this discussion deals with primary petroleum solvents, free of nonpetroleum additives, further reference to such additives is not pertinent. In this case the most useful criterion for classifying the material is the boiling range (A.S.T.M. [American Society for Testing Materials] distillation test), and this characteristic should be included in any inspection of the material under investigation.

There are few branches of manufacturing in which the use of solvents is not indispensable. In previous communications [1] the importance of some solvents as a cause of occupational dermatoses was emphasized.

CLINICAL STUDY

Our purpose is (1) to determine by patch tests variation in reaction to kerosene, mineral seal oil, spindle oil and intermediate fractions in order to determine which classes of petroleum products exert irritant action on the skin and the limits above which such irritant action would not be likely to occur; (2) by pointing out the correlation between the boiling range of the solvent and the results of patch tests, to indicate somewhat the limit of primary irritability and the possibility of individual sensitivity to products above this limit, and (3) finally to discuss the practical applications of this study.

It is generally recognized that the more viscous fractions of petroleum, free of additives, exert no irritant action on the skin. In fact, such fractions sufficiently refined serve as bases for emollients, protective creams and cosmetics. On the other hand, the more volatile fractions of petroleum have been shown to be primary cutaneous irritants and to exert a defatting action on the skin. Some writers have expressed the opinion that the irritation is entirely the result of this defatting action. However, positive reactions to patch tests with spindle oils of a boiling range and viscosity of the same order as lubricants used in emollients indicate that more is involved than action of a physical solvent, unless it is argued that these viscous oils also exert a solvent action. This point might well be worthy of investigation.

It can be stated, generally, that all products in class I (boiling ranges below 450 F.) are primary cutaneous irritants. Generally speaking, it may also be said that all products in class III (boiling ranges above 600 F.) exert no irritant action. Class II (boiling ranges between 350 and 600 F.) includes materials which give conflicting

1. (*a*) Klauder, J. V.: Actual Causes of Certain Occupational Dermatoses: A Study of Five Hundred and Twenty-Seven Cases, with Special Reference to Dermatoses Due to Mineral Oils, Arch. Dermat. & Syph. **48**:579-600 (Dec.) 1943. (*b*) Klauder, J. V., and Hardy, M. K.: Actual Causes of Certain Occupational Dermatoses: II. A Further Study of Fve Hundred and Thirty-Two Cases, with Special Reference to Dermatitis Caused by Certain Petroleum Solvents, Occup. Med. **1**:168-181 (Feb.) 1946.

results in patch tests, representing, perhaps, a "twilight zone" of irritability. It is on these materials that clinical study was performed.

Persons Tested.—Patch tests were performed on the following groups:[2] Group I included normal (healthy) persons, both white and

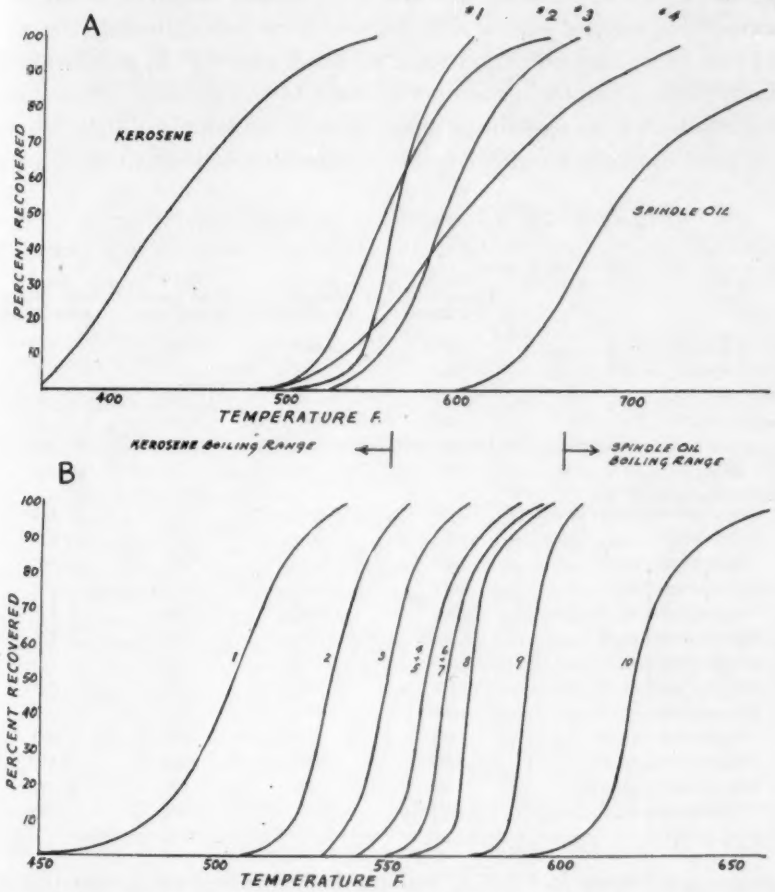

Chart 2.—*A*, boiling ranges of mineral seal oils. *B*, boiling ranges of 10 per cent fractions of mineral seal oil no. 1.

Negro, not regularly exposed to petroleum products. Group II included industrial workers whose dermatitis was attributed to petroleum solvents used in their work. Group III consisted of patients with diffuse

2. In performing patch tests, a piece of four ply gauze 1 inch (2.5 cm.) square was used. In each test 6 drops of the solvent or oil was applied to the gauze, covered with wax paper and maintained at the site for twenty-four hours. Positive reactions were graded as follows: mild erythema 1 plus, well defined erythema 2 plus, erythema with edema and with or without a few vesicles 3 plus and erythema, edema and many vesicles or serous exudation 4 plus.

lesions of eczematous dermatitis. Of these patients, the dermatitis of some was caused by external contact (nonallergenic) and of others there was no evidence of such cause.

Petroleum Products Tested.—Tests were performed with two samples of kerosene, one of paraffinic and one of naphthenic origin; four samples designated as mineral seal oil and obtained from four different refineries —(1) an East Coast refinery, from a paraffinic source; (2) a midwestern refinery, from a paraffinic source, (3) and (4) two different West Coast refineries, both from naphthenic sources—and one sample of light spindle oil of predominantly paraffinic origin. Inspection data obtained on these

TABLE 2.—*Physical Properties of Mineral Seal Oils*

	No. 1, East Coast, Paraffinic	No. 2, Midwest, Paraffinic	No. 3, West Coast, Naphthenic	No. 4, West Coast, Naphthenic
Specific gravity at 60 F.....	0.8833	0.8398	0.8681	0.8822
A. P. I. gravity at 60 F.....	28.3	37.0	31.5	28.9
Color, Saybolt.....	+16	+18	+19	—2
Flash point, F.....	275	260	—	—
Kinematic viscosity, centistokes...	4.20 at 100 F.	5.20 at 100 F.	9.36 at 100 F.	9.81 at 100 F.
Pour point, F.....	20	20	—	—
Distillation (A. S. T. M.)				
Initial boiling point, F.....	506	498	530	480
End point, F.....	607	654	667	700+
5% recovered at, F.....	537	...	552	530
10% recovered at, F.....	544	523	556	538
20% recovered at, F.....	551	532	569	555
30% recovered at, F.....	556	541	577	572
40% recovered at, F.....	559	549	584	586
50% recovered at, F.....	563	557	592	602
60% recovered at, F.....	568	566	600	620
70% recovered at, F.....	574	576	608	640
80% recovered at, F.....	580	589	618	660
90% recovered at, F.....	590	606	642	695
95% recovered at, F.....	605	...	665	...

samples are shown in table 2, and the boiling range characteristics are presented graphically in chart 2 *A*. Tests were also performed with 10 per cent fractions of sample I mineral seal oil (table 3). The boiling range characteristics of these fractions are discussed later.

Patch Tests with Kerosene.—Kerosene was tested only on persons comprising group I. All of 20 white persons reacted to kerosene from a paraffinic source: 2 had 1 plus reactions, 2 had 2 plus reactions, 10 had 3 plus reactions and 6 had 4 plus reactions. Of 14 Negroes tested, 6 reacted negatively, 7 had reactions of 2 plus or less and only 1, a mulatto, had a 4 plus reaction.

Kerosene commercially available in the eastern part of the United States is all of paraffinic origin. To determine the relative irritant

action of a naphthenic fraction of the same boiling range, a sample was specially prepared from a naphthenic crude petroleum and refined in the conventional manner employed for paraffinic distillates of kerosene. Tests were performed with this naphthenic kerosene on 10 normal (healthy) white persons. All reacted positively, and 7 had 4 plus reactions. Of persons tested (white as well as Negro) with both types of kerosene, the reaction to the naphthenic fraction was greater.

This study evidences a varying tolerance of the skin of white persons to paraffinic kerosene, a greater tolerance of the skin of Negroes and a greater irritant action of naphthenic kerosene compared with that of

TABLE 3.—*Ten Per Cent Fractions from Mineral Seal Oil No. 1*

	No. 1 0-10 %	No. 2 11-20 %	No. 3 21-30 %	No. 4 31-40 %	No. 5 41-50 %	No. 6 51-60 %	No. 7 61-70 %	No. 8 71-80 %	No. 9 81-90 %	No. 10 91-100 %
Specific gravity at 60 F.....	0.8309	0.8324	0.8314	0.8324	0.8324	0.8328	0.8328	0.8328	0.8358	0.8463
A. P. I. gravity at 60 F.....	38.8	38.5	38.7	38.5	38.5	38.4	38.4	38.4	37.8	35.7
Kinematic viscosity, centistokes at 100 F.....	2.75	3.43	3.93	4.28	4.39	4.57	4.54	4.74	5.47	7.50
Distillation (A. S. T. M.)										
Initial boiling point, F.....	436	510	532	540	544	548	553	559	575	588
End point, F.....	534	553	570	584	586	594	583	585	603	663
5% recovered at, F.....	474	520	536	547	550	558	560	568	584	611
10% recovered at, F.....	483	524	540	556	553	560	562	570	585	614
20% recovered at, F.....	492	527	544	558	555	562	564	571	587	616
30% recovered at, F.....	498	530	546	560	557	564	565	572	588	618
40% recovered at, F.....	502	532	548	560	559	566	566	573	589	620
50% recovered at, F.....	506	534	550	562	561	568	567	574	590	621
60% recovered at, F.....	510	536	552	564	563	570	569	575	592	623
70% recovered at, F.....	514	539	554	566	565	573	570	576	593	626
80% recovered at, F.....	519	542	557	568	569	576	572	577	595	631
90% recovered at, F.....	525	547	562	574	576	584	577	580	598	643
95% recovered at, F.....	530	550	566	578	581	590	580	583	600	662

paraffinic. The latter observation is consistent with the observation of Jordan [3] that the irritant action of petroleum compounds is increased by the presence of naphthenes (polymethylene compounds).

Patch Tests with Mineral Seal Oil and Light Spindle Oil.—In a communication [1a] by one of us (J. V. K.) report was made of dermatitis from mineral seal oil. It was stated: "In these patients the dermatitis was clinically of the sensitization type, appearing on the hands and forearms and in some on the face, usually months after initial exposure." Patch tests with mineral seal oil gave positive reactions on these patients and negative results on 8 persons used as controls. For this reason it was concluded that mineral seal oil was not a primary irritant.[4] Sub-

3. Jordan, O.: The Technicology of Solvents, New York, Chemical Publishing Company, 1937.

(Footnotes continued on next page)

sequent study (now reported), in which a larger number of normal persons were used for patch tests, warrants the changing of this opinion that dermatitis from mineral seal oil is an allergic reaction. Evidence now suggests that such dermatitis represents a primary irritant action, appearing, for the most part, in workers whose threshold became lowered after continuous exposure.

Thirty white persons (group 1) were tested with the aforementioned four samples of mineral seal oil. The results in percentage of positive reactions were as follows: sample 1, 60; sample 2, 63.3; sample 3, 43.3 and sample 4, 12.9.

Of the positive reactions with samples 1 and 2, the 2 plus and 3 plus reactions predominated, whereas with samples 3 and 4 the predominating reactions were 1 plus and 2 plus.

Of 20 persons tested with light spindle oil, 15 per cent reacted positively, in all of whom the reactions were 1 plus.

In interpretation of these results, attention should be directed to the differences in the characteristics of the boiling range of the four samples of mineral seal oil [5] (table 2 and chart 2*A*). Sample 1 is nearest to kerosene, samples 3 and 4 are practically light lubricating oils approach-

4. The mineral seal oil used for testing these 8 persons was sample 1, used in the study now reported. As later discussed, 18 of 30 white persons subsequently tested with this sample reacted positively. The records of the 8 controls tested in the previous report were reviewed. It was noted that in 1 of these the reaction was 1 plus and in another a questionable 1 plus. At the time of the original study these minor reactions were disregarded. In the light of present results on a larger number of persons these minor reactions assume a greater significance. This emphasizes the difficulty of evaluating minor reactions in studies with patch tests if a small number of persons is used. Apropos, from a statistical standpoint, is the question of how many persons should be given patch tests to justify a conclusion that the substance tested is not a primary irritant.

This is discussed in the following papers: Henderson, C. R., and Riley, E. C.: Certain Statistical Considerations in Patch Testing, J. Invest. Dermat. **6**:227-230, 1945, and Knudsen, L. F.: A Note on the Statistical Probabilities of Finding Hypersensitive Subjects in Random Samples, ibid. 231-232. "If no positive reactions occur in 100 subjects, the rate of positive reactions in the population is not likely to exceed approximately 2.9%, the likelihood being at the 95% level; and that if one reaction is observed in 100 subjects, the likelihood is 95% that the rate does not exceed approximately 4.5%."

Error of judgment was more inherent to ignoring the two minor reactions in the group of 8 persons tested than in the small number employed. We do not believe that patch tests performed on a larger number of persons than were employed in the study now reported would affect the validity of our conclusions, although the percentage of incidence of positive reactions would be somewhat changed.

5. The quality of mineral seal oil apparently varies among different refiners. There is no accepted trade standard of what constitutes mineral seal oil. Federal specification VV-0-391, Oil; Illuminating (mineral seal oil with a boiling range of 300 F.), sets no limits for boiling range or viscosity, placing primary emphasis on burning characteristics in a lamp.

ing spindle oil and sample 2 is intermediate. These petroleum products are on the borderline between volatile solvents and lubricants. The greatest percentage of positive reactions occurs with the samples (1 and 2) having the lowest boiling range. The higher incidence of positive reactions with these samples can be attributed to their proximity to the boiling range of kerosene. The result is what would be expected in a blend of kerosene and lubricating oil, which mineral seal oil is to all intents and purposes.

The proportion of kerosene in the blend correlates primary irritant action. Conversely, mineral seal oil samples 3 and 4 are blends containing relatively small proportions of kerosene. Their irritant action approaches the relative immunity of lubricating oil (light spindle oil).

We also conducted studies by patch tests with a petroleum solvent obtained from a cracking process employed in obtaining high octane gasoline. The boiling range of this solvent corresponded essentially to that of kerosene, but its chemical composition reflected a high aromatic content approaching coal tar distillates. This solvent would have a high solvency for many materials for which the solubility in ordinary kerosene would be limited. Patch tests on normal persons uniformly gave 4 plus reactions. This greater irritant action suggests that solvency or defatting action is intimately associated with cutaneous irritation. The greater irritant action of this solvent (of high aromatic content) did not correlate with the boiling range. The correlation of boiling range with irritant action applies to the paraffinic type of petroleum products and not to naphthenic or highly aromatic products whether derived from petroleum or other sources.

Although patch tests were not performed with petroleum solvents of boiling ranges below those of kerosene, we believe, from clinical experience, that such solvents, in contrast to kerosene, would produce more uniformly severe reactions and that, in contrast to mineral seal oil, all persons would react.

It is of interest to note that cutaneous reaction to paraffinic kerosene varies only qualitatively. As the boiling range increases, the reaction varies both quantitatively and qualitatively and becomes considerably attenuated in the boiling range of light spindle oil.[6]

Tests with four samples of mineral seal oil and with light spindle oil were performed on industrial workers.

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6. From clinical experience, prolonged exposure to light spindle oil does not suffice to cause dermatitis. This is in contrast to mineral seal oil of boiling ranges corresponding to samples 1 and 2. Wedroff and Dolgoff (Zur Frage der Pathogenese der Ölacne, Arch. f. Gewerbepath. u. Gewerbehyg. **6**:428-436, 1935) concluded from their observation of workers exposed to mineral oil (lubricating oils) of the naphthenic type that the incidence of eczematous dermatitis was no greater than its incidence in general. In Hopf's (Ueber gewerbliche Oelschädigungen der Haut, Aerztl. Sachverst. Ztg. **43**:229-241, 1937) observation, dermatitis from mineral oil (lubricating oils) was not common except in eczematic persons.

The dermatitis (usually on the hands and forearms) of the workers in group 2 appeared after variable periods of exposure either to mineral seal oil or to other petroleum solvents such as kerosene or Stoddard solvent. In some the solvent was not identified; in others the properties of the mineral seal oil were not known. The interval between the first exposure and onset of dermatitis was variable—weeks (infrequently), months, usually one year or longer or, in some, as long as twenty to thirty years. Conspicuous among these workers were pressmen and their helpers who clean printing presses with a petroleum solvent of a boiling range of kerosene or lower.[1b] The number of workers tested with each sample varied from 15 to 39.

The results in percentage of positive reactions were as follows: sample 1, 92.3; sample 2, 100; sample 3, 66.6; sample 4, 47.3, and light spindle oil, 72.3. Of positive reactions with samples 1 and 2, the 2 plus and 3 plus reactions predominated.

The smaller percentage of positive reactions to sample 4 compared with that to spindle oil is a discrepancy. Sample 4 of mineral seal oil approaches the boiling range of light spindle oil; yet the percentage of positive reactions to patch tests was less than that of spindle oil. This discrepancy may be related to the hydrocarbon composition of these oils. In these persons a lowered threshold to paraffinic oils, of which light spindle oil is an example, has developed. Samples 3 and 4 are naphthenic. Therefore the reaction to these oils is nearer to that of the normal skin as in group I.

Patch Tests with 10 Per Cent Fractions of Mineral Seal Oil.—Since samples 1 and 2 of mineral seal oil produced a large proportion of positive reactions in persons comprising groups I and II, an effort was made to determine which part of their boiling range was chiefly responsible for this high incidence. A portion of sample 1 was refractioned by distillation through a fractionating column, being separated into 10 per cent fractions. Each fraction was inspected in the laboratory, and the characteristics of the ten fractions are shown on table 3 and chart 2 *B*. It should be noted that the first five fractions (50 per cent of mineral seal oil) fall largely within the boiling range of kerosene. Fractions representing 51 to 90 per cent fall between the end point of kerosene and the initial boiling point of spindle oil, while the last 10 per cent falls entirely within the boiling range of spindle oil.

Patch tests were performed with these ten fractions on 35 white persons (group I) and on workers with dermatitis caused by solvents (group II). The number of workers (group II) tested with each fraction was 45. The results in percentage of positive reactions (1 to 4 plus), starting with fraction 1 and in the order written to fraction 10, were as follows:

Group I: 100, 100, 82.8, 80, 77.7, 60.0, 57.0, 40.0, 22.7, 11.4.
Group II: 100, 100, 100, 95, 92.5, 90.2, 90.2, 87.8, 84.8, 70.7.

In both groups the incidence of positive reactions was greatest in the fractions within the kerosene range and least in the fractions approaching lubricating oil.[7] The degree of positive reactions was consistent with the incidence. Three plus reactions in tests with the first five fractions predominated, whereas 2 plus and 1 plus reactions predominated in tests with fractions 6 to 10. The observation that irritant action on the skin of the paraffinic type of petroleum products decreases as the boiling range increases is similar to observations on solvent action, which likewise is in inverse ratio with the boiling range. Since the results obtained with highly naphthenic and highly aromatic products do not correlate with the results obtained with paraffinic products, the correlation of boiling range cannot be applied to these materials. In view of the higher solvency of the naphthenic and aromatic solvents, it is possible that the increased irritant action reflects a heightened defatting action. There is also the possibility that it is a reflection of chemical toxicity.

The varying tolerance of the normal skin as noted in patch tests with paraffinic kerosene was again apparent with the ten fractions in the study of persons in group I. The individual variation was considerable; it ranged from 1 plus to 2 plus reactions to only the first two or three fractions to a varying degree of positive reactions to all ten fractions (4 patients).[8] This variation could not be correlated with complexion. Not all persons who reacted to many or to all of the ten fractions were blonds; conversely, not all who reacted to only the first few fractions were dark complexioned.

Patch tests with the ten fractions were also performed on 18 Negroes. The incidence of positive reactions was considerably less than that of white persons. Frequently there was no reaction. (It is possible that slight erythema could not be seen on the darker-skinned Negroes.) Many had 1 plus reactions only to the first two or three fractions. The most pronounced result (in a mulatto) was 1 plus and 2 plus reactions up to fraction 6.[9]

7. A few workers included in group II whose dermatitis was presumably caused by petroleum solvents reacted only to the first four or five fractions. This apparently opposed solvent as a cause; at the same time such reaction was not that of an eczematic skin. An allergic causation of the dermatitis in these patients was therefore suggested, but it could not always be proved. If the dermatitis was caused by solvents, apparently then the skin of the back, the site of the patch tests, did not share in the lowered tolerance.

8. This emphasizes how relative is the term "primary irritant." What should be the concept of a primary irritant? Should it connote the reaction of an individual or reaction of all persons tested? Definitions in vogue envisage one or the other of these meanings. The difference, of course, is relation to what is the "normal" reaction of the skin. The word "normal" itself has been so much abused that some teachers request students not to employ it.

(Footnotes continued on next page)

It is to be noted that the percentage of positive reaction (but not the degree of reaction) to the ten fractions and also to the mineral seal oils (samples 1 to 4) and to spindle oil was appreciably greater in persons comprising group II than in white persons in group I. This evidences a lower tolerance not only to the solvent which gave rise to the dermatitis but to paraffinic petroleum products of higher boiling range, extending into the range of lubricating oils.[10]

As discussed in the foregoing paragraphs, there is evidence that lowered tolerance to paraffinic products is not reflected in a comparable degree to naphthenic products (samples 3 and 4 of mineral seal oils) of the approximate boiling range. This suggests a chemical specificity.

Since the degree of positive reactions was not greater than that observed on normal persons, an allergic hypersensitivity can be excluded. In order to determine whether the lower tolerance was specific for petroleum products or existed for all external irritants, an expression of the eczematic skin, the following study was performed.[11]

Eighteen patients in group II who reacted to all or to almost all the ten fractions were given patch tests with the following eczematogenous noxae: 50 per cent turpentine in olive oil, 5 per cent solution of formaldehyde, 0.5 per cent potassium dichromate, tincture of iodine, 5 per cent ammoniated mercury in petrolatum, 1 per cent ammonium fluoride and 1 per cent sodium arsenate. The dermatitis of these patients varied in degree; it affected only the hands in some; in others it affected the hands, forearms and arms. The reactions to the eczematogenous noxae were variable, ranging from reaction to only a few of the noxae to reaction to the majority. The percentage of positive reaction to each noxae varied from a minimum of 27 per cent (tincture of iodine) to 75 per cent (0.5 per cent potassium dichromate).

As a control study, 20 patients with eczema (group III) were given patch tests with the ten fractions and also with the aforementioned eczematogenous noxae. Eleven of the 20 patients reacted to all ten fractions. Negative reactions were obtained only with fractions 8, 9

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9. These observations are consistent with knowledge that the skin of Negroes is less susceptible to external irritants. Dr. Sidney Repplier, of the Curtis Publishing Company, informs us that the incidence of dermatitis from solvents used to clean printing presses is considerably less among the Negro employees.

10. It would be of interest to note at what point in the range of viscous petroleum products this lower tolerance is no longer apparent.

11. One phase of our purpose was to exclude possibility of impaired function of the skin in combating defatting action of solvents, comparable to impaired function to neutralize alkali. As a result of his studies, Burckhardt (Beiträge zur Ekzemfrage: die Rolle des Alkali in der Pathogenese des Ekzems speziell des Gewerbeekzems, Arch. f. Dermat. u. Syph. **173**:155, 1935; Das Maurerekzem [Eine experimentelle und klinische Studie zur Ekzemfrage] ibid. **178**:1, 1938) attributed such impairment as a cause of dermatitis due to alkali. He designated it toxic hypersensitivity in contrast to allergic hypersensitivity.

and 10. The percentage of positive reactions to the eczematogenous noxae was not essentially different than that of patients in group II.

Since patients with eczematous dermatitis (group III) reacted to the ten fractions in a manner comparable to patients with dermatitis caused by solvents (group II), it appears that the dermatitis of such patients (group II) is not the expression of a hypersensitivity solely to such solvents. Petroleum solvents apparently are eczematogenous noxae, comparable to other noxae, prolonged exposure to which lowers the threshold of irritability of the skin, predisposing to a nonspecific irritability of the skin (eczematous dermatitis).[12]

Practical Applications of These Studies.—The foremen of some of the workers who had dermatitis from exposure to petroleum solvents have frequently remarked that other workers doing the same work have never had dermatitis. It is to be noted, however, that the period of exposure to solvents in the group of 45 workers with dermatitis extended up to thirty years. The observation that the general run of industrial workers are apparently immune to petroleum solvents is consistent with the varying reaction to patch tests of normal persons comprising group I. Of practical importance is the question: Will dermatitis eventually develop in all workers exposed to solvents?[13]

To reduce the hazard of dermatitis from petroleum solvents, it is desirable, provided gloves or other mechanical protection cannot be employed, to use a solvent with as high a boiling range as is consistent with the purpose for which it is to be used. Mineral seal oil (of the same boiling range as sample 1) should be given preference to kerosene; spindle oil of high viscosity should be preferred to one of low viscosity. For some industrial uses (for example, the cleaning of printing presses) rapid solvent action is an important requisite. Therefore solvents of high boiling range may not be appropriate. This, however, may not apply to other work entailing exposure of the hands to solvents (for example, the cleaning of mechanical parts). Kerosene of paraffinic origin should be preferred to one of naphthenic origin. In previous studies[1] it was stated that "A conspicuous mechanism of the acquisition of dermatitis was the use of solvents . . . to clean mechanical parts,

12. The employment of the ten fractions for patch testing affords a standardized qualitative manner of determining tolerance of the skin to external irritants. For this reason they are preferable to the commonly employed eczematogenous noxae.

13. This is concerned with predisposing causes of occupational dermatoses and is in relation to circumstances that alter the physiology and defensive mechanism of the skin. There is evidence that an increase in degree of exposure to a noxae or injury to the skin, such as a burn, predisposes to dermatitis. The defensive mechanism of the skin is doubtless dependent on an interplay of a number of physiologic functions, which, in turn, are altered by a variety of factors such as diet, fatigue and hygiene of the skin.

the article of work or containers such as ink and paint cans. Usually small parts were immersed by hand into a solvent without the use of gloves. This was done by machinists, machine operators and a variety of other workers." For this purpose mineral seal oil may suffice or a mixture of kerosene and mineral seal oil.

Practical Application of Patch Tests with the 10 Per Cent Fractions.—It is well known that a patch test performed with a petroleum solvent with a low boiling point is of limited value. By virtue of its primary irritant action a positive result can be predicted. Our studies suggest that a solvent with the boiling range of kerosene or lower will uniformly give a positive reaction to a patch test.

Patch tests performed with a number of solvents having ascending boiling ranges, comparable to the ten fractions employed in this study, are a means of determining the tolerance of the skin to paraffinic petroleum solvents. Such a series of tests has a practical application, since it is a means of selecting persons whose cutaneous tolerance to solvents is high. A high tolerance would be indicated by reactions only to the first two or three fractions, in contrast to all or to the first seven or eight. A less accurate way of determining tolerance is a single patch test performed with kerosene. We observed that reaction to kerosene varied from 1 to 4 plus. The degree of reaction to kerosene corresponded, in the majority of persons tested, with the number of positive reactions obtained with the ten fractions.

If patch tests with the ten fractions were employed in selecting persons for work entailing exposure to solvents, it would doubtless eliminate the workers in whom after short exposure dermatitis develops. Such tests, however, would not prevent dermatitis apparently caused by lessened tolerance inherent to prolonged exposure and to an increased degree of exposure.

As discussed in the foregoing paragraphs, positive reaction to all or almost all the ten fractions is characteristic but not diagnostic of dermatitis caused by petroleum solvents. On the other hand, positive reactions to only the first one half or less of the ten fractions is evidence against such cause of dermatitis. This is illustrated in the following case:

In a man operating a grinder exposing his hands and forearms to soluble cutting oil, there developed dermatitis affecting these areas. A solvent in the oil was suspected. No accurate information was available as to its composition. Its physical appearance was that of a light spindle oil. Reactions to patch tests with this oil and the four samples of mineral seal oil were negative. The reaction to the ten fractions was as follow:

	Numbers								
1	2	3	4	5	6	7	8	9	10
1+	1+	1+	—	—	—	—	—	—	—

This study evidenced a high degree of tolerance to petroleum solvents, opposing solvent causation of the dermatitis, and excluded an allergic reaction to the oil

to which he was exposed. Further questioning elicited the likely cause of the dermatitis. For years he used Oakite for cleansing. The powder was applied freely on the palms and then rubbed over the hands and forearms. After recovery, we counseled his return to the same work with cessation of this method of cleansing.

Patch tests with the aforementioned ten fractions were of value in differentiating dermatitis due to petroleum solvents from that arising as an allergic reaction to oil, as illustrated in the following case:

A young woman was employed for two years inspecting ball bearings. With ungloved hands she immersed the bearings in a pan containing light spindle oil and then in a pan containing kerosene. Dermatitis first appeared on her arms, which she attributed to contact with her soiled hands when she stood with arms folded across her chest. Subsequently the hands, forearms, face, neck and V of the chest became affected. Involvement of the face and neck suggested an allergic reaction. This was supported by patch tests. The ten fractions reacted as follows:

Numbers									
1	2	3	4	5	6	7	8	9	10
2+	1+	1+	1+	—	—	—	—	—	3+

Negative results were obtained with the four samples of mineral seal oil. The slight reactions to the ten fractions were inconsistent with dermatitis arising from kerosene. On the contrary, they evidenced a good degree of tolerance. The 3 plus reaction to fraction 10 suggested an allergic reaction to spindle oil. The dermatitis promptly disappeared after cessation of work. On the basis of these patch tests we counseled her return to work entailing exposure to petroleum solvents but not to spindle oil.

SUMMARY

1. Report is made of results of patch tests with petroleum solvents and oils essentially of paraffinic origin ranging from kerosene (initial boiling point 345 F.) to light spindle oil (end boiling point 840 F.) performed on normal white persons, Negroes, industrial workers with eczematous dermatitis caused by petroleum solvents and patients with eczematous dermatitis not caused by solvents.

2. There is a correlation between the boiling ranges of petroleum products of paraffinic origin and their irritant action. Irritant action like defatting action decreases as the boiling range increases.

3. Petroleum solvents with boiling ranges up to and including kerosene are primary irritants. This may or may not be due entirely to their defatting action.

4. The cutaneous reaction to petroleum oils with boiling ranges intermediate between kerosene and the viscous lubricants varied considerably in normal persons, from no reaction to varying degrees of positive reactions. The skin of the Negroes showed a high degree of tolerance. There was a lessened degree of tolerance of the skin of workers with dermatitis caused by solvents and of patients with dermatitis not caused by solvents.

5. Cutaneous reaction to kerosene of naphthenic origin and to a solvent of high aromatic content obtained from a cracking process employed in obtaining high octane gasoline was much greater than that of solvents of paraffinic origin with the same boiling range. With the former products defatting action or chemical toxicity might be the cause of increased irritant action.

6. The amount of individual tolerance to petroleum oils and solvents can be determined by patch tests with ten distillation fractions with different boiling ranges, extending from that of kerosene to that of light spindle oil.

7. Dermatitis caused by petroleum solvents is regarded as the expression of a nonspecific sensitivity comparable to dermatitis from exposure to other eczematogenous noxae.

8. Practical application of this study is discussed.

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ABSTRACT OF DISCUSSION

DR. LOUIS SCHWARTZ, Bethesda, Md.: Dr. Klauder and Mr. Brill are to be congratulated for their fine paper. Such experimental work should be encouraged. First, I want to make clear that mineral seal oil is a cutting oil used for light cutting operations. They have proved by experiments what my colleagues and I have observed in industry and taught to our classes from another viewpoint, namely, that the irritant properties of various pretroleum distillates are directly proportionate to their fat solvent properties and that the latter are inversely proportionate to their viscosities, all other factors being constant. The paper brings out the fact that even the last of the ten fractions, which is an oil, caused 11.4 per cent of reactions in the control group, showing that even the oily fractions have a primary irritant action on certain types of skins. We have found that this irritant action occurs mostly on dry skins or senile skins, which cannot rapidly replace the fat which the oil takes out. For this reason we state that mineral oils should not be used as ointment bases, either cosmetic or medicinal, on dry skins and that they make good bases for oily skins.

The last of the ten fractions caused reactions on 70.7 per cent of the workers who had dermatitis and worked with these oils. This high incidence of positive reactions to patch tests is explained by the fact that these workers showed by their dermatitis that amoung them predominated the types of skin which cannot stand defatting, namely, dry skin or senile skin. The 29.3 per cent of the patients with dermatitis who had no reactions to the patch tests either had dermatitis from some of the additives in the oils with which they worked or did not have occupational dermatitis, or their dermatitis may have been caused by the accumulation of the continued action of large quantities of the oils occupationally encountered, conditions not present in the patch tests.

The increased susceptibility of dry skins to the action of fat solvents can be regarded as a hypersensitivity due to an anatomic and physiologic defect of the skin and not as an allergy. An allergy of the skin denotes to me a change in the reactivity of the body fluids or cells induced by exposure to an allergen, which manifests itself by a dermatitis on a reexposure to the same or a similar allergen.

Allergy is highly specific. In the case of solvent dermatitis, any of the classes of solvents would cause similar dermatitis in the case of patients with dry skins.

As the authors bring out one must not lose sight of the fact that, under actual occupational conditions, these petroleum distillates are often treated with sulfur and chlorine compounds when made into actual cutting oils and that to these sulfurized, chlorinated bases other chemicals—called additives—are added in order to give certain desirable properties to the cutting oils. Some of these additives, such as the chlorinated hydrocarbons (carbon tetrachloride, chloronaphthalenes and chlorodiphenyls) and the phenolics (inhibitors) are themselves primary irritants and sensitizers. Moreover, the heat generated at the point of the cutting tool often forms decomposition products, such as SO_2 and H_2S, which are irritants; finally, the alloy of which the cutting edge is made contains sensitizing metals, such as cobalt, and as the edge of the tool wears away the oil will contain them.

The fat solvent properties of the petroleum distillates are only one of the factors by which they as a class cause dermatitis. It is true that this is the principal cause of dermatitis from the low boiling fraction, but they also have keratogenic and sensitizing properties. The type of dermatitis caused by the low boiling fractions is usually of the eczematoid type, either acute or chronic, on the hands and forearms. The acute type occurs chiefly on the fingers, interdigital spaces and dorsa of the hands, and the chronic type occurs on the palms as well. Petroleum distillates with high boiling points have less defatting action but more keratogenic action. They cause comedos, acnes, photosensitivity, melanosis, keratoses and epitheliomas. The oils from various portions of the globe differ in these keratogenic properties; for instance, the oils derived from Scotch shale have greater carcinogenic properties than our American oils, hence the higher incidence of "mule-spinners' cancer" in England. Twort stated that the degree of fluorescence of an oil is an index of its carcinogenic properties. Benzopyrene is said to be the principal carcinogen in petroleum oils.

The heat of the fractional distillation and of the cracking process forms certain irritant chemicals which were not in the original crude oil, and these chemicals remain mostly in the final heavy oils and the residual tars, asphalt and pitch. While epithelioma, melanosis and photosensitivity will develop in only a small proportion of workers, our experience in industry shows that dermatitis, folliculitis, comedos and acne from petroleum distillates will develop in any one if there is sufficient exposure and lack of proper protectives and lack of scrupulous cleanliness.

I do not advocate preemployment patch tests for new workers who are to work with petroleum solvents. Patch tests can only pick out the workers whose skins are already predisposed to dermatitis. Patch tests are not necessary to do this. Such dry or senile skins can be seen at a glance by an experienced physician. Moreover, if a person with a dry or senile skin uses proper protective clothing, proper emollient protective creams and scrupulous cleanliness he can avoid dermatitis. In workers having oily, thick skins, who may not react to the patch test, dermatitis will in time develop if they do not take the proper preventive precautions because as they get older their skin becomes dryer. Continued exposure to the solvents, exhausts and injures the glands in the skin. Comedos and acnes are more likely to form on oily skin which passed the preemployment patch test, from continued exposure; finally, epithelioma is more likely to develop in older workers regardless of the results of preemployment patch tests. An observant dermatologist can tell by inspection the type of skin which can best withstand

the action of the various petroleum distillates, but he cannot stop time and prevent a young worker with such a skin from becoming an older worker with a vulnerable skin.

DR. HARRY J. TEMPLETON, Oakland, Calif.: This scientific investigation into a relatively unexplored field is of the excellence that one expects and always gets in Dr. Klauder's papers. It is unfortunate that the time allotted did not permit him to give many details which we who were permitted to read the paper obtained.

When one first reads this paper and looks at all the charts, it seems rather technical, but further study shows its great practicability. For example, manufacturers might be able to reduce the incidence of oil dermatitis or entirely eliminate it by changing from some of the light oils of low boiling point and higher irritability to some of a higher boiling point and a low irritability, or they might change from the irritating oils of the naphthenic series to the less irritating oils of the paraffin series. These two points alone make the paper practical.

I doubt somewhat the actual practical value of preemployment routine patch tests of applicants with the various fractions of mineral seal oil. In the first place, I do not think that employers will go to the trouble of doing this.

In the second place, I think that there is at least a theoretic danger of sensitizing patients to certain fractions. From my own experience, I should warn against the use of the full strength oils of the lower boiling range in patch tests. Earlier in my experience, I blistered some patients unmercifully by so doing and even produced second degree burns with some of the fractions, such as Stoddard solvent and kerosene.

During the war, my colleagues and I here in the San Francisco Bay district saw a great deal of industrial dermatitis in general and oil dermatitis in particular, as did all dermatologists. Because of this great problem, several committees began the study of industrial dermatitis and oil dermatitis. One was from the United States Public Health Service, one from this Section on Dermatology of the American Medical Association, and one from the American Dermatological Association.

Having served on Dr. Schwartz's Committee of the United States Public Health Service, I can testify to the valuable work that he and his group in Washington are doing on this problem of oil dermatitis. This would be expected when one remembers that he has dermatologists, physicists, mycologists, chemists and botanists at his command and that he and his staff have the utmost experience in the field work, which goes on right out into the factory. However, as I have sat in on those conferences, I have been impressed by the fact that the knowledge that his group gains is not sufficiently widely disseminated, and it occurs to me that there ought to be a closer relationship—a liaison of some kind—between the committees for the United States Public Health Service and the committees from the American Medical Association and the American Dermatological Association, which are composed of the practical dermatologists throughout the country who are doing a great deal of the industrial dermatology. I make it as a suggestion that these committees pool their findings; otherwise something will be lost.

DR. J. V. KLAUDER, Philadelphia: The percentage of positive reactions to patch tests performed with fractions 1 to 10 included all reactions from 1 to 4 plus. The figures that Dr. Schwartz quoted, percentage of positive reactions to the last fraction, comprised all 1 plus reactions. It is to be noted that this reaction was produced after twenty-four hour contact of the patch; since the material

tested was oil, no evaporation occurred. It is to be doubted whether the 1 plus reactions have any practical significance.

The degree of positive reactions correlated the range of the fractions. Two and 3 plus reactions predominated, with some 4 plus reactions in the tests with fractions 1 to 5, whereas 2 plus and 1 plus reactions predominated in the tests with 6 to 10.

Briefly, our study showed that the irritant action correlated the boiling range; as the boiling range increased, the irritant action decreased. The defatting action is also in inverse ratio with the boiling range. It is to be emphasized that the correlation of irritant action with the boiling range applied to petroleum products of paraffinic origin. Irritant action of kerosene of naphthenic origin and of a solvent of high aromatic content obtained from a cracking process employed in obtaining high octane gasoline was much greater that that of solvents of paraffinic origin with the same boiling range. We believe that this is not generally known.

An interesting question suggested by our studies is this: Can a solvent be produced that exerts a minimum defatting action on the sebum in the direction of minimizing irritant action on the skin?

CUTANEOUS DIPHTHERIA

Two Unusual Cases with Eruptions Resembling Lymphogranuloma Venereum and Ectodermosis Erosiva Pluriorificialis

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DESPITE the high frequency in China of diphtheritic infections of the upper respiratory tract, not a single case of cutaneous diphtheria has hitherto been reported. This fact may be understood better if one considers the large number of clinical manifestations which are caused by the bacilli. On the other hand, the importance of cutaneous diphtheria has been little stressed in the past on account of its rare occurrence, and because one seldom observes the typical false membrane type of disease on the skin. Moreover, it should be emphasized that the occurrence of a great many varieties makes even more difficult recognition at first glance of the true nature of the eruption. It is, however, of paramount importance, especially from an epidemiologic point of view, to suspect cutaneous diphtheria whenever a pustular eczematous ulcerative process does not yield to ordinary treatment, and when lesions show a preference for certain localizations.

CLINICAL MANIFESTATIONS

The clinical picture is varied, and among the many varieties described the false membrane type is still known as the most characteristic. To attach a diagnostic significance principally to the formation of pseudomembranes is erroneous, as other cutaneous diseases also produce pseudomembranes without having any relationship to diphtheria. Wound diphtheria, as a postoperative complication, is dreaded by all surgeons. This, like other diphtheritic infections of the skin, is difficult to diagnose without bacteriologic investigation, unless postdiphtheritic complications (palsy, for example) give a warning sign. Otherwise, the granulating wounds do not always show suspicious changes such as formation of dirty-looking adherent membrane, the removal of which is difficult and is followed by profuse bleeding. Moreover, the wound may not show any increased inflammatory reaction, and, despite this, along the necrotic undermined borders is a steady spreading of the ulceration. The ulcerative type has been fairly well recognized, and one should suspect diphtheria as a cause when punched-out ulcers appear suddenly, espe-

From the Division of Dermatology and Syphilology, National Medical College, Shanghai (Chief of Service: Frederick Reiss, M.D.).

cially in children. Intertriginous localization makes such a suspicion even more justified. The eczema-like type ranges next to it in frequency. In children the combination of retroauricular eczema with rhinitis, conjunctivitis and otitis should always be thought of as a diphtheritic syndrome. In other instances perioral and periocular eczema is associated with conjunctivitis and rhinitis, a combination highly indicative of a diphtheritic cause. Diphtheritic eczema may be localized in the genital region or, in rare instances, may affect the external auditory canal alone. Impetiginous, impetiginous-eczema-like, ecthymatous, vesicular and bullous types have also been reported. Among the rarer types are eruptions resembling dermatitis herpetiformis, tumor and abscesses.

During the years 1938 to 1941 closer attention has been paid in the clinic of the National Medical College of Shanghai to cutaneous diphtheria. Among 18,644 new cases of cutaneous disease (from July 1938 to September 1941) 9 cases (0.38 per cent) have been recognized culturally, and, also, the virulence test proved in all instances a high degree of pathogenicity. Among the 9 cases virulent bacilli from the throat and from the nose could be cultured in only 1 instance. Six were of the ulcerative variety, 1 was impetiginous, 1 was of the ecthyma type and 1 presented lesions in a child which clinically could hardly be differentiated from lymphogranuloma venereum, an infection which rarely occurs in children. The ninth case was observed in the European Refugee Isolation Hospital and presented a sudden appearance of periorificial ulcerations, a picture rather suggestive of ectodermosis erosiva pluriorificialis.

REPORT OF CASES

Case 1. —W. C. H., a girl of 4, was brought in by her parents on Dec. 24, 1938 with a history of masses in both inguinal regions for nearly three months. The masses steadily increased in size and were painless. They were incised two months previous to her visit, when a thick whitish material was evacuated. Her parents noticed a small ulcerative lesion between the labia majora one month after the onset of the inguinal swelling, which disappeared in one week's time. It broke out again and remained for the two months. Swelling throughout the external genitalia was present for over one week. The patient was well developed and well nourished and did not appear to be sick. Local examination revealed a purplish red swelling of the vulva with sensation of resistance on palpation over the surrounding tissue. The inner surfaces of the left labium majus and labium minus were irregularly ulcerated, with a slight amount of discharge. Discharging sinuses and ulcers were found in the inguinal regions. The patient's father had had a bubo in the left inguinal region four years before, but his reaction to the Frei test was doubtful, and that of her mother was negative. Laboratory data showed the following blood count: red blood corpuscles 4,800,000; white blood corpuscles 23,600, with 76 per cent polymorphonuclear leukocytes, 18 per cent small lymphocytes, 2 per cent large lymphocytes, 2 per cent monocytes and 2 per cent myelocytes. Smears and cultures, except hemolyltic streptococci, did not suggest pathogenic organisms. Reactions to repeated Frei tests (three antigens) were negative. Treatment consisted of sulfanilamide administered orally and compresses of lotion of

lead acetate administered locally, under which the patient showed slow but steady improvement. The affected parts became soft, and the edema subsided substantially. On account of the unsatisfactory therapeutic result cultures were made for diphtheria bacilli with positive results. Diphtheria antitoxin (5,000 international units) was given immediately, after which the child disappeared from observation until a return visit on March 9, 1939. On this visit the child's temperature was 38.3 C. (100.94 F.), and inguinal and vulval lesions were about the same. The tonsils were enlarged and congested. The patient had a high temperature and died that very night (at home), probably of toxemia.

Case 2.—Mr. F. F. (fig. 1), a 30 year old German refugee, came to the hospital on Oct. 28, 1940 in a feverish condition lasting two days. Before the onset of the fever he had a painful sensation in the left inguinal region and a sort of tension in the vicinity of the mouth. On November 3, I was called in consultation, and on examination I observed in the left inguinal region a 10 by 4 cm., irregularly outlined,

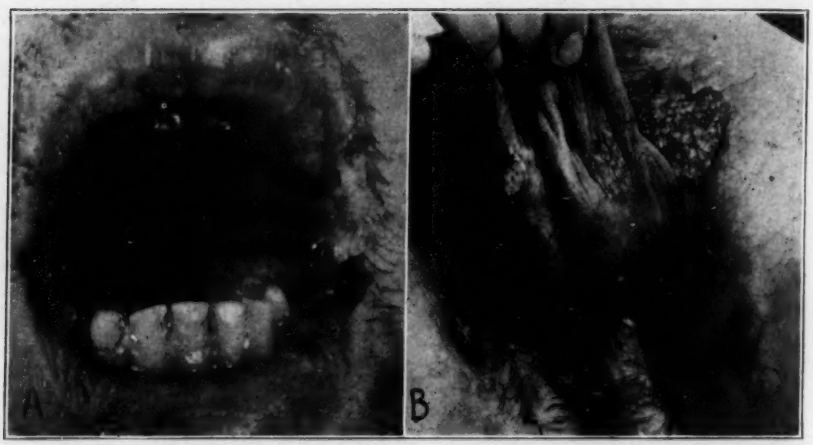

Fig. 1.—*A*, a bean-sized ulcer in the vicinity of the left angle of the mouth. *B*, extensive ulcerations in the right inguinal region and smaller ulcers on the scrotum and in the right crural region.

shallow sore, which was covered with bloody crusts. On several places on the scrotum were bean-sized lesions, and on the right side of the thigh were several shallow ulcerations with partly undermined borders. On the lower lip in the vicinity of the left angle of the mouth was a painful ulcer the size of a horse bean, which was covered with a fibrinous exudate. In the vicinity of the left nostril a similar lesion was found. In view of the sudden onset, with the initial temperature of 37.8 C. (100.04 F.) reaching 38.2 C. (100.76 F.) three days after admission and, furthermore, with the sudden appearance of periorificial pseudomembranous lesions, the possibility of ectodermosis erosiva pluriorificialis was considered. A blood count showed 4,700,000 red blood corpuscles and 7,600 white blood corpuscles. The Wassermann and the Kahn reaction of the blood were negative. A blood culture for diphtheria bacilli was negative. Smears were made from the lesions which revealed a palisade-like arrangement of diphtheroid bacteria, which the culture and the virulence test proved to be of the virulent diphtheritic type. The same observations were made and the same results were obtained from the nose and from the throat on November 17 and on December 6. A biopsy was made, and the histo-

logic examination revealed the following (fig. 2): The epidermis and part of the cutis were replaced by an ulcerative process and were bordered by acanthotic epidermis. The floor of the ulcer was covered with necrotic material, leukocytes and cellular and nuclear detritus. There was, furthermore, a diffuse fibrinous exudate which extended to the cutis. The collagenous fibers were loosened, and, besides numerous leukocytes, there were a great many red blood corpuscles around dilated blood vessels.

The treatment consisted of local application of antidiphtheritic serum and of azosulfamide ointment and administration of 6,000 units of diphtheria antitoxin. Under this treatment the sores became cleaner, and healthy granulations replaced

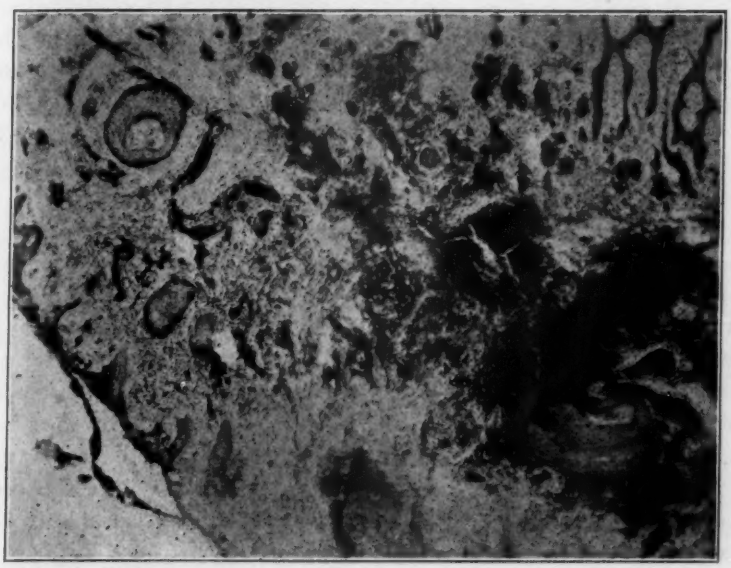

Fig. 2.—Showing the necrotic process involving the subcutis with deeply staining fibrinous exudate and cellular debris.

the dirty membrane and the ulcerations. Complete recovery was achieved on November 30. Cultures from the throat and from the nose done on December 2 proved to be negative.

DIFFERENTIATION OF THE DIPHTHERIA BACILLI AND THE PSEUDODIPHTHERIA BACILLI

Although from the staining (bipolar bodies, palisade-like arrangement of bacilli) one can gain certain information of the character of diphtheria bacilli, the culture, the biochemical reactions and the virulence test are more exact. The method of Martin and Loiseau [1] is not quite so reliable as claimed, because often there is only a surface growth on dextrose agar stab cultures, and yet the growth may prove to be diph-

1. Cited by Calmette, A.; Boquet, A., and Nègre, L.: Manuel technique de microbiologie et sérologie, ed. 3, Paris, Masson & Cie, 1933.

theria bacilli. This is borne out by my experience. The Costa-Troisier method is based on the acid formation of diphtheria bacilli on dextrose agar, whereby with the help of an indicator colonies of diphtheria bacilli appear rose, whereas colonies of pseudodiphtheria remain grayish. This method proved reliable in my cases. Besides the routine virulence test I investigated a method, communicated personally by Prof. H. Raubitschek, which consists of the following procedure: From a twenty-four hour diphtheria culture a saline suspension is made (5,000,000 organisms in 1 cc.) from which 0.5 cc. is mixed with 0.5 cc. of isotonic solution of sodium chloride, and in another tube 0.5 cc. bacterial emulsion is mixed with 0.5 cc. diphtheria antitoxin. Both tubes are kept for two hours in incubators at 37 C. after which 0.2 cc. from each suspension is injected intradermally into the right and the left abdominal wall respectively. When there was diphtheritic infection the injection of the bacterial-saline mixture would produce severe hyperemia and necrosis after twenty-four to forty-eight hours, but no reaction on the side where the antitoxin-bacterial emulsion was injected. This can be confirmed by my experiments, but in addition it should be remarked that animals tested with virulent diphtheria bacilli died after thirty-six hours. In instances of pseudodiphtheria both sides would produce hyperemia and necrosis. From a practical point of view, the determination of virulence should be demanded in order to rule out pseudodiphtheritic bacilli infections, 50 per cent of which are present on the normal skin. Eller and Kest [2] claimed that diphtheria bacilli "have a varying virulence for different species and even for the same species." According to these authors the degree of virulence may be variable, so that the virulence test may show only the degrees of virulence but does not differentiate true diphtheria from pseudodiphtheria.

From an epidemiologic point of view it is necessary to adhere to a strict differentiation between diphtheria bacilli and pseudodiphtheria bacilli, and for that reason attention should be drawn to the clinical picture of cutaneous diphtheria. The purpose of the article was not so much to describe two rare types of cutaneous diphtheria as to emphasize the commoner forms of the disease. Cutaneous diphtheria has been the cause of serious spreading of diphtheria of the throat, because it has not been recognized in time. One of the most striking examples is the case reported by Boas [3] of impetigo-like conditions in a 1 year old child, which later proved to be diphtheria, and which infected in the same ward 4 other children, 3 nurses, 1 male attendant and 1 female attendant. When one observes in Shanghai the many instances of

2. Eller, J. J., and Kest, L. H.: Eczema of the Ear Associated with a Diphtheria-Like Organism, Arch. Dermat. & Syph. **44**:1020-1022 (June) 1940.

3. Boas, L.: Diphtheria der Haut, Zentralbl. f. Haut- u. Geschlechtskr. **33**: 27, 1930.

innocently acquired cases of syphilis among children, one can well imagine the role cutaneous diphtheria may play in spreading the disease, especially since diphtheria bacilli can remain virulent on dead material for more than eighteen months.

COMMENT

The 2 reported cases are undoubtedly unusual in their clinical appearances. Although from tumor-like swellings virulent diphtheria bacilli have been isolated by Müller [4] from the pus of an inguinal abscess, not a single instance is on record of similar clinical manifestations of lymphogranuloma-venereum-like diphtheria. One of the commonest and most characteristic symptoms in diphtheria of the vulva in children, the retention of urine, was absent in my case (case 1) as was the usual bloody discharge. The absence of these symptoms was sufficient cause not to suspect diphtheria bacilli. Therefore, there was ground to consider lymphogranuloma venereum. However, thorough investigation proved the infection to be caused by diphtheria bacilli.

The second case bore all the characteristics of ectodermosis erosiva pluriorificialis, a disease with an infinite variety of clinical symptoms but characterized by sudden rise of temperature, rapid appearance of perioral and perianal erosions and ulcerations often coupled with conjunctivitis, rhinitis and diphtheroid stomatitis. While I do not propose to enter into discussion of the cause of ectodermosis erosiva pluriorificialis here, it is my contention that this syndrome suggests a bacterial intoxication, which may be in some rare instances caused by diphtheria bacilli. The only case which bears some similarity to this one is reported by Santori,[5] who described a "rather unusual" appearance of multiple intertriginous pseudomembranous ulcerations in the genital and in the retroauricular region, all of which proved to be caused by virulent diphtheria bacilli.

CONCLUSION

Two unusual types of cutaneous diphtheria are reported. One resembles lymphogranuloma venereum and the other ectodermosis erosiva pluriorificialis. In one case the upper respiratory tract contained diphtheria bacilli, and in the other it did not. The isolated bacilli were highly virulent.

Attention is drawn to the importance of early recognition of cutaneous diphtheria from an epidemiologic point of view.

816 Fifth Avenue.

4. Müller, J. E.: Seltene durch den Diphtheriebazillus hervorgerufene Erkrankungen, Deutsches Arch. f. klin. Med. **109**:583, 1913.

5. Santori, G.: Primäre Hautdiphtherie mit vielfachen Herden, Dermat. Wchnschr. **110**:367, 1941.

ECZEMATOUS SENSITIZATION

A Review of Its Immunologic Properties and Some Speculations as to Its Nature

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WHEN the living organism comes into either external or internal contact with a foreign substance a variety of alterations may ensue. One of these is a subtle change in the body's economy, which is not immediately manifest, so that on again meeting the substance the organism presents an altered reactivity to it. This altered reactivity is what is termed the allergic reaction, and when this state of altered reactivity has developed, the organism is said to be sensitized. There are, however, different possible varieties of sensitizations of which at least three appear to be distinct immunologic entities. These are: (1) the anaphylactic (of which I regard the atopic as a part), (2) the tuberculin or bacterial and (3) the eczematous variety. It is with this last variety that this paper deals.

NATURE OF THE SUBSTANCES WHICH YIELD ECZEMATOUS SENSITIZATIONS

In considering the nature of the substances which elicit eczematous sensitizations it seems necessary to distinguish between eczematous sensitizations which arise spontaneously and those which are deliberately produced. The materials which yield eczematous sensitizations spontaneously are almost legion in number, as any practicing dermatologist knows, but the substances with which one can produce an eczematous sensitization deliberately are far more restricted in number. In both cases they are relatively simple compounds, usually of known chemical configuration. In fact, when the actual eczematous allergen has been isolated from complex mixtures, such as the juices of the Chinese primrose or poison ivy, the allergen has turned out to be a relatively simple compound, such as primin (empiric formula: $C_{14}H_{18}O_3$ or $C_{14}H_{20}O_3$) in the primrose and a compound closely related to n-pentadecyl catechol in poison ivy. There appears to be a definite correlation between the capacity of substances for regularly causing eczematous

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sensitization and the chemical configuration of these substances. In the case of the nitrochlorobenzenes, Landsteiner and Jacobs [1] have shown a reasonable and definite correlation between the sensitizing ability of a particular nitrochlorobenzene and the reactivity of a chlorine atom or a nitro group. They stated as follows:

> In most cases a correspondence was evinced between lability of Cl and NO_2, when treated with alkali, and sensitizing effects; and in all cases tested there was agreement between ability to sensitize and formation of substitution compounds with an organic base. It seems reasonable to assume that in the animal a reaction takes place by which substances are converted into antigens. How and with what substances, proteins or others, a combination of the active compounds occurs, remains to be ascertained.

In the case of other compounds which are good sensitizers, such as paranitrosodimethylaniline and paraphenylenediamine, different types of reactions with the bodily constituents are to be expected, but it seems not unreasonable to believe that a correlation exists between the ability of the compound to sensitize and its ability, or the ability of its breakdown products, to enter into combination with some of the body substances. This question is discussed in somewhat greater detail in a recent article by Gell and his colleagues.[2] The reason that persons acquire eczematous sensitizations to a much wider variety of substances than can be used to produce these sensitizations experimentally is not known. The explanation probably lies in the persons rather than in the chemicals. There may be some peculiar genetic predisposition to sensitizations in general or to the allergen in question in particular (Landsteiner, Rostenberg and Sulzberger [3]), or there may have been some special favoring circumstance at the time the allergen was encountered, such as a local inflammation.

SITE TO WHICH THE ALLERGEN MUST BE APPLIED

Ordinarily in the development of spontaneous eczematous sensitization the allergen comes into contact with only the epidermis or possibly the external mucous membranes, and in view of the fact that eczematous sensitizations do not seem to arise from the vast majority of substances which are taken internally the question naturally arises whether the allergen must come into contact with the epidermis in order for eczematous sensitization to be engendered. In spontane-

1. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds: II., J. Exper. Med. **64**:625, 1936.

2. Gell, P. G. H.; Harington, C. R., and Rivers, R. P.: The Antigenic Function of Simple Chemical Compounds: Production of Precipitins in Rabbits, Brit. J. Exper. Path. **27**:19, 1946.

3. Landsteiner, K.; Rostenberg, A., Jr., and Sulzberger, M. B.: Individual Differences in Susceptibility to Eczematous Sensitization with Simple Chemical Substances, J. Invest. Dermat. **2**:25, 1939.

ously developing sensitizations it is practically impossible to study this question. We therefore have to turn to experimental sensitization. The first investigators in this field observed that unless the material was applied to the epidermis they did not get eczematous sensitization. Sulzberger [4] was unable to sensitize guinea pigs to neoarsphenamine when the allergen was administered intramuscularly, intraperitoneally, intrapulmonally, intratesticularly or intracardially. The same pigs were subsequently sensitizable by intradermal injection of neoarsphenamine. Straus,[5] working with newborn infants, was unable to get sensitizations [6] by subcutaneous injection or by feeding of Rhus extract, whereas he easily succeeded (73 per cent of 48 infants) when the substance was applied to the skin. Simon,[7] in working with guinea pigs, observed that a good eczematous allergen, such as poison ivy, would not yield eczematous sensitization if it was injected intramuscularly, intravenously or intraperitoneally. In the older literature there were some reports on the successful development of eczematous sensitization when the allergen was given extraepidermally, but in none of these cases were any special precautions taken to avoid cutaneous contamination. The first experiments which employed careful technic and yet succeeded in producing eczematous sensitization by an extraepidermal route were those of Landsteiner and Chase.[8] These investigators observed that if they injected picryl chloride intraperitoneally they would occasionally get an eczematous sensitization but that the results were not constant and the sensitizations which did develop were of low intensity. If

4. Sulzberger, M. B.: Arsphenamine Hypersensitiveness in Guinea-Pigs: II. Experiments Demonstrating the Role of the Skin, Both as Originator and as Site of the Hypersensitiveness, Arch. Dermat. & Syph. **22**:839 (Nov.) 1930.

5. Straus, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, J. Allergy **5**:568, 1934.

6. He did get sensitization in 1 case out of 10 cases in which the ivy extract was given by subcutaneous injection, but, as he states, it is difficult to be certain that the skin was not contaminated. It must be remembered that extraordinarily minute amounts will suffice to yield eczematous sensitization, particularly if one is working with concentrated material. My colleagues and I have found that in experiments in which we were endeavoring to avoid cutaneous contamination, when we used 2,4 dinitrochlorobenzene, we would usually think we had been successful, whereas, when we worked with paranitrosodimethylaniline we would usually be aware of contamination. The difference between the substances is, of course, that paranitrosodimethylaniline is a highly colored material and minute traces are easily visible, whereas 2,4 dinitrochlorobenzene is colorless. To offset this inherent difficulty with solutions of 2,4 dinitrochlorobenzene, in experiments of this character we now add a dye to the solution.

7. Simon, F. A.: Observations on Poison Ivy Hypersensitiveness in Guinea Pigs, J. Immunol. **30**:275, 1936.

8. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: VII. Skin Sensitization by Intraperitoneal Injections, J. Exper. Med. **71**:237, 1940.

they concomitantly injected tubercle bacilli they consistently caused sensitizations of high intensity. They concluded: "It follows that although skin sensitization of this type is most easily obtained by dermal application this route of administration is no necessary condition for such sensitivity." The word "type" refers to "contact dermatitis type," the expression which the authors used in the sentence previous to the one quoted here. Gell [9] observed that animals would experience cutaneous sensitization to tetryl (N-methyl-ar,N-tetranitroaniline) from subcutaneously implanted pellets made of tetryl. In fact, he achieved better sensitizations with this method than with intradermal injections. Sulzberger, Baer and Kanof [10] have noted that BAL (2,3 dimercaptopropanol) would yield sensitizations when applied to the skin by various technics and also when injected intramuscularly. The authors expressed the belief that the sensitization developed is not of the classic eczematous type, but the arguments which they adduce for this contention do not to me seem particularly convincing. In neither Gell's work nor in the work of Sulzberger and his associates were any particular precautions taken to avoid cutaneous contamination. It would thus appear that the easiest route by which eczematous sensitization can be achieved is by application of the material to the epidermis, but that does not mean that this is an essential route.[11] Why the application of the allergen to the epidermocutis should be better for the production of eczematous sensitization than the giving of the material by other routes can only be surmised, but, in my opinion, it is correlatable with the macrophage content of the tissue of conjugation and with the physical nature of the conjugate (soluble or not). These points will be discussed subsequently in the article.

WHAT HAPPENS TO THE ALLERGEN AT THE SITE OF APPLICATION?

In the naturally developing eczematous sensitization the material is applied to the epidermocutis, and consequently we are interested in

9. Gell, P. G. H.: Sensitization to "Tetryl," Brit. J. Exper. Path. **25**:174, 1944.

10. Sulzberger, M. B.; Baer, R. L., and Kanof, A.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): V. Skin Sensitization to BAL, J. Clin. Investigation **25**: 488, 1946.

11. Actually, the term "epidermis" in this connection is not strictly correct inasmuch as eczematous sensitizations are achieved just as well by intradermal injections, which, as is well known, are not intraepidermal. Consequently, whether it is the epidermis or the cutis or both which participate in the reaction is unknown. In this article the terms "epidermocutis" and "epidermocutaneous" will be used to indicate that from the point of view of eczematous sensitization the epidermis or the cutis or the junction of the two is regarded as an immunologic unit and that the two are not, in the present state of knowledge, immunologically dissociable.

what happens to the allergen at this site. There would seem to be four theoretic possibilities: (1) that the allergen stays in situ, (2) that the allergen disseminates through or over the epidermis, (3) that the allergen is absorbed as such or (4) that the allergen reacts locally and a new substance is absorbed. Considering first the possibility that the allergen stays in situ, this implies that the sensitization is manufactured in the epidermocutis and that antibodies or some equivalent sensitizing materials are manufactured locally. At the termination of the incubation period then, these antibodies well over, so to speak, and by some means get to all the epidermocutis cells, so that the entire integument participates in the sensitivity. This moment is often indicated by a flare-up at the site of application of the allergen. This hypothesis is refuted by the work of Landsteiner and Chase [12] and of Simon,[7] who have shown that the site of application of the antigen in the case of poison ivy can be extirpated any time after the twelfth or twenty-fourth hour, respectively, and that the development of eczematous sensitization proceeds unhampered. Obviously, unless sensitization was already present at the time of extirpation it could not become generalized from excised skin. That the organism is not sensitive at this time is easily demonstrated by cutaneous tests, reactions to which are, as a rule, not positive until the sixth day, rarely earlier but not in any case at the twenty-fourth hour. The second possibility is that the allergen traverses the surface of the epidermis or disseminates through the epidermis via the prickle cell bridges or that it dissolves in a lipoidal material in the epidermis, thereby reaching the individual epidermocutis cells and by its presence causing them to develop the specific alteration in reactivity. While this is a theoretic possibility, it seems to be irreconcilable with two experimental facts. First, Landsteiner and Chase [12] and Schnitzer [13] have shown that if the allergen is applied to a cutaneous island which is made so as to sever completely all epidermocutaneous connections the generalization of the sensitization is not interfered with. Furthermore, Schnitzer [13b] has shown that a certain minimal concentration per unit of cutaneous area is required in order to induce eczematous sensitization and that if the simple allergen were distributed as previously mentioned there would be no need for this requirement. The third possibility, that the simple allergen is absorbed,[14] while it cannot be said to be completely disproved, is, in my opinion, extremely

12. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: VI. Experiments on the Sensitization of Guinea Pigs to Poison Ivy, J. Exper. Med. **69**:767, 1939.

13. (*a*) Schnitzer, A.: Untersuchungen über den Ausbreitungsmechanismus der ekzematösen Sensibilisierung, Dermatologica **83**:70, 1941; (*b*) Beitrag zur Frage des Mechanismus der Sensibilisierung, ibid. **85**:339, 1942.

14. By "absorbed" I mean that the allergen in its original form gets to the site where the hypersensitive state is induced.

improbable for two main reasons: 1. The chemical nature of the eczematous sensitizers makes it unlikely that these substances could traverse any considerable amount of tissue without reacting. 2. A certain minimal concentration is required per unit of cutaneous area. There would not seem to be any reasonable explanation for this if the allergen itself were absorbed, for in this case one would think that the total amount would be the determining factor, whereas it is quite conceivable that in order to effect certain chemical interactions a requisite minimal concentration must be present. We are thus reduced to the conclusion that the eczematogenous allergen when applied to the epidermocutis reacts there to form a new compound allergen. The nature of this allergen is unknown, but the work of Landsteiner and Jacobs [1] and of Gell and his colleagues [2] make it appear likely that the new allergen is a protein conjugated with the simple chemical or with some derivative of it.

ROUTE BY WHICH THE COMPOUND ALLERGEN LEAVES THE SKIN

The question of the route by which the compound allergen leaves the skin has not been entirely settled but has been subjected to various experimental attacks with rather conflicting results. Landsteiner and Chase [12] endeavored to settle this question by making cutaneous islands in guinea pigs. Their technic consisited of isolating an area of epidermis so that its epidermal continuity had been severed and its continuity with the rest of the animal was via the blood vessels and the lymphatics, which run in the layer known in the guinea pig as the panniculus carnosus. (This layer overlies the superficial musculature.) If they applied their sensitizing allergen to the island and tested off the island they observed that the generalization of the sensitization depended on the integrity of the panniculus carnosus. If they cut through the panniculus carnosus the sensitization did not become generalized, whereas, if they did not cut the panniculus carnosus, it became generalized. Schnitzer,[13] in two studies on this point, was unable to corroborate these observations and noted that he did get generalization irrespective of whether or not he cut the panniculus carnosus. In some experiments which, however, differed in two important technical respects from the experiments of Landsteiner and Chase, I [15] observed that the cutting of the panniculus carnosus did not interfere with the generalization of sensitization.[16] These various experiments, while not settling the role

15. Rostenberg, A., Jr.: Studies on the Eczematous Sensitization: I. The Route by Which the Sensitization Generalizes, J. Invest. Dermat., to be published.

16. It should be pointed out that in the technic of making a cutaneous island complete lymphatic isolation is not achieved even though the panniculus carnosus is cut, inasmuch as there are some lymphatics that communicate directly from the posterior surface of the island to deeper structures. The exact number of these lymphatics will depend on the size of the island and on its location.

of the lymphatics in the generalization of sensitization, certainly exclude the hypothesis that the generalized sensitivity is achieved because the allergen dissolves in and spreads through an epidermal lipoidal substance (Straus and Coca [17]), or that the allergen or the antibody disseminates by passing intraepidermally from prickle cell to prickle cell (Schreiber and Müller [18]). I believe that the compound allergen is probably absorbed primarily via the lymphatic channels but that other routes are also possible.

SITE OF THE DEVELOPMENT OF HYPERSENSITIVITY

Unfortunately, there is practically nothing known concerning the site of the development of hypersensitivity in the case of the eczematous sensitization. All that is known is that some time, usually six to nine days after the application of the sensitizing agent, the entire epidermis, as a rule, becomes sensitive. Just where or how this alteration in sensitivity is effected is not known. It can be stated, on the basis of the work previously referred to, that this alteration does not take place in the epidermis. From the evidence that a likely route of the absorption from the skin is via the lymphatic channels, it would appear that at least some of the material goes to the regional lymph node. This would be a reasonable site for the manufacture of sensitivity inasmuch as it is fairly well established in other types of immune reactions that antibodies are manufactured in the regional node (Ehrich and Harris [19]).[20]

17. Straus, H. W., and Coca, A. F.: Studies in Experimental Hypersensitiveness in the Rhesus Monkey: III. On the Manner of Development of the Hypersensitiveness in Contact Dermatitis, J. Immunol. **33**:215, 1937.

18. Schreiber, W., and Müller, W.: Grundlegender Versuch zur Klärung der Frage, auf welchem Wege sich die Sensibilisierung in der Epidermis ausbreitet, Dermat. Wchnschr. **107**:1393, 1938.

19. Ehrich, W. E., and Harris, T. N.: The Formation of Antibodies in the Popliteal Lymph Node in Rabbits, J. Exper. Med. **76**:335, 1942.

20. There is much dispute in modern immunologic literature as to the relative role of the lymphocytes, macrophages and plasma cells in the formation of antibodies. As an amateur in this field, I can but hazard a guess, and that is that all three play a role, the relative importance in a given case being determined by the nature of the antigen. Literature on the role of the lymphocytes has been previously cited. Mention should also be made of the work of A. White and T. F. Dougherty (The Role of Lymphocytes in Normal and Immune Globulin Production, and the Mode of Release of Globulin from Lymphocytes, Ann. New York Acad. Sc. **46**:859, 1946). The role of macrophages has been treated by F. R. Sabin (Cellular Reaction to a Dye Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67, 1939), and on the role of the plasma cells by M. Bjørneboe, H. Gormsen and F. Lundquist (Further Experimental Studies in the Role of Plasma Cells as Antibody Producers, J. Immunol. **55**: 121, 1947).

EXISTENCE OF ANTIBODIES IN ECZEMATOUS SENSITIZATION

The existence of antibodies in eczematous sensitization is a point that has been much debated for a considerable number of years, and the bulk of opinion until very recently was that there were no humoral antibodies in this type of sensitization. It is well established that humoral antibodies of the nature of the Prausnitz-Küstner antibody are not present in eczematous sensitization. The specificity of the reaction, however, makes it likely that an antigen-antibody mechanism exists. It has been hypothesized that there were antibodies but that they were sessile and fixed to the epidermal cells and consequently could not be demonstrated in the circulation. Urbach and Koenigstein [21] conceived the idea that if one could damage these cells so as to liberate these antibodies and at the same time entrap them, it should be possible to demonstrate their existence. They therefore devised their cantharides technic, and they have claimed many successful transfers of epidermal sensitization by means of this technic. Recently, Landsteiner and Chase [22] succeeded in obtaining successful passive transfers by means of cellular exudates and bits of tissue obtained from lymph nodes and spleens of sensitized animals. It would thus appear that the sensitizing material is contained within the lymphocytes (and possibly other cells) and that when these sensitized lymphocytes are transported the sensitization is passively transferred. This may explain some of the successful Urbach-Koenigstein transfers, in that, fortuitously, a large number of cells were contained in the blister fluid, and these cells contained the sensitizing bodies. Further evidence for the existence of some sort of humoral sensitizing substance is contained in two experiments by Haxthausen.[24] The first experiment was made with 2 sets of identical twins, (1) A and B and (2) X and Y. A and X were sensitized to 2,4 dinitrochlorobenzene. An area of skin was interchanged between A and B and between X and Y, so that an area of skin from the sensitized A was in a nonsensitive B, and similarly for X and Y. After the grafts had taken, the subjects were tested both outside the grafted area and on the grafted area. In A there was a positive reaction both outside and inside the graft area, whereas in B there was no reaction outside or inside the graft area, and similarly

21. Cited by Urbach, E., and Gottlieb, P. M.: Allergy, ed. 2, New York, Grune & Stratton, Inc., 1946, p. 150.

22. Chase, M. W.: The Cellular Transfer of Cutaneous Hypersensitivity, J. Bact. **51**:643, 1946. Landsteiner, K., and Chase, M. W.: Experiments on Transfer of Cutaneous Sensitivity to Simple Compounds, Proc. Soc. Exper. Biol. & Med. **49**:688, 1942.

23. Footnote deleted by author.

24. Haxthausen, H.: The Pathogenesis of Allergic Eczema Elucidated by Transplantation Experiments on Identical Twins, Acta dermat.-venereol. **23**:438, 1943; The Occurrence of Humoral Antibodies in Allergic Eczema Investigated Through Parabiosis Experiments on Guinea Pigs, ibid. **24**:286, 1943.

for X and Y. In other words, the skin from the sensitized person did not react in its new environment, whereas the skin from the nonsensitive person reacted in its new environment. Haxthausen interpreted this as showing that the sensitivity could not reside in the epidermis or it would be carried along with it, which it was not, and that there must be some humoral influences at work which caused the nonsensitive skin of B and Y to react in their new environment of A and X. The second experiment consisted of sensitizing a guinea pig and then connecting it by abdominal parabiosis to a normal pig. It was observed that the second pig also became sensitive. He interpreted this as corroborating the conclusion drawn from his previous experiment that there must be humoral influences at work which carry the sensitization. I believe that these experiments of Haxthausen's offer strong inferential evidence for the existence of some sort of humoral agency which is capable of transferring eczematous sensitization. These experiments do not shed any light on the question whether this humoral agency exists free in the tissue fluids or is carried intracellularly, as by lymphocytes.

SHOCK TISSUE AND THE SITE OF THE REACTION

The evidence favors the view that the epidermocutis is the shock tissue. The reasons for this belief are that clinical manifestations seem to be confined to the epidermocutis, and rarely do other tissues participate. For example, persons who are sensitive to poison ivy can, as a rule, chew the leaves with impunity. Jadassohn [25] has reported cases of epidermal sensitivity to iodoform in which the iodoform could be inserted intravaginally or into an ulceration and in neither case cause any reaction provided that it was applied carefully so as not to let any iodoform come into contact with the epidermis. Whether the manifestations of sensitization are as strictly limited to the epidermocutis in eczematous sensitization brought about by the extraepidermal introduction of the allergen is unknown.

SOME SPECULATIONS AS TO THE MEANING OF THE IMMUNOLOGIC FACTS

So far I have given some immunologic facts known about eczematous sensitization. It now remains to be seen whether these facts can be welded into a consistent whole. Obviously, any theory in the present state of knowledge is destined to have but a short life; however, its justification is that it may serve to point the way for further research. There are two points about eczematous sensitization which especially

25. Jadassohn, J.: A Contribution to the Study of Dermatoses Produced by Drugs, in Selected Essays and Monographs, London, New Sydenham Soc.,1900, no. 170, p. 207.

require elucidation. These are: (1) Why is the application of the allergen to the epidermocutis a superior route for the engendering of the sensitization and (2) what is the nature of the antibody in the sensitization and wherein does it differ from other more easily demonstrable antibodies?

In regard to the reason that application to the epidermocutis is a superior route, Sabin [20] has shown by direct evidence from the injection of an antigenic dye that the true cutis is distinctly richer in macrophages than is the subcutis, and, so far as I can gather, it is also richer than muscle. I have already referred to the fact that Landsteiner and Chase got no sensitizations or poor ones when they introduced picryl chloride intraperitoneally but good sensitizations when they concomitantly introduced tubercle bacilli. While a final opinion cannot be expressed, it seems probable that the adjuvant effect was achieved for the reason that the authors state: "In a general way, more rapid mobilization and modified activity of macrophages under the influence of tubercle bacilli —there is even greater phagocytic capacity for inert particulate matter— have been taken to be responsible for the effects mentioned." I therefore believe that the allergen has to be deposited in an area relatively rich in macrophages in order to effect an eczematous sensitization and that this is not the case when the material is given subcutaneously or intramuscularly. This, however, would not explain the failure when the allergen is given intraperitoneally or intravascularly. Here I believe that a different explanation has to be invoked. Landsteiner and Chase [26] failed to get cutaneous sensitization when they injected conjugates made with picryl chloride and either horse or guinea pig serum, but they succeeded [27] when they used conjugates made with picryl chloride and the stromas of guinea pig erythrocytes. What is the difference between these two conjugates? I believe that the essential difference is that the first is soluble and the second is not. Dr. Elmer L. Becker and I, in some unpublished observations (as yet on a preliminary scale), have succeeded in getting cutaneous sensitization to 2,4 dinitrochlorobenzene in the guinea pig by using either cutaneous or renal conjugates made in vitro with 2,4 dinitrofluorobenzene. The material was injected intraperitoneally and contained both soluble and insoluble fractions. It is certainly conceivable that the body handles particulate material and antigens differently. If this assumption is correct, then, of course, the failure to get eczematous sensitization with intravenous injection is explained. With intraperitoneal injection the situation is

26. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: IV. Anaphylaxis Induced by Picryl Chloride and 2,4 Dinitrochlorobenzene, J. Exper. Med. **66**:337, 1937.

27. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: IX. Skin Sensitization Induced by Injection of Conjugates, J. Exper. Med. **73**:431, 1941.

somewhat more complicated, as there probably are both soluble and insoluble conjugates formed, so that the material by itself yields a poor or not any sensitization. When an adjuvant which yields a good macrophage response is used, this may serve two purposes: (1) as a source of cellular (insoluble) material for conjugation and (2) as a source of phagocytes to take up the conjugate. Actually, the macrophages may pick up the simple chemical directly, and the conjugation may be intracellular. In view of the fact that sensitizations can be achieved with conjugates made in vitro, this does not seem likely.

The second point needing clarification is the nature of the eczematous antibody. The salient feature of this antibody is that it apparently does not exist free in the circulation. This may be correlatable with the fact that the full antigen incorporates a part of the body's protein into its being. As a result, when the antibody is manufactured a portion of its specificity is directed against the protein which participated in its formation. Because of this protein specificity the antibody would attach to tissue containing this protein. It is further postulated that this attachment constitutes the state of being sensitized but that a reaction becomes manifest only when the allergen (probably as the simple chemical) comes along to complete the reaction. I believe that in order to get a reaction in a sensitized animal, the substance used in the test has to be able to unite with the tissues in a way that the sensitizer did. Dr. E. L. Becker, who collaborated with me on a modified form of this theory, and I observed that the application of conjugation. It is thus seen that sensitive animals do not react if the skin of pigs that were sensitized to 2,4 dinitrochlorobenzene failed to cause reactions (unpublished). Further, animals that are sensitized to 2,4 dinitrochlorobenzene will not react to m-dinitrobenzene, which is presumably the part of the 2,4 dinitrochlorobenzene molecule left after conjugation. It is thus seen that sensitive animals do not react if the simple allergen is already conjugated or if it has been modified so that it can no longer conjugate.

CONCLUSION

The eczematous sensitization is brought about by the interaction of chemical compounds having the ability to form protein conjugates with certain of the body constituents. Ordinarily these protein conjugates are formed in the epidermocutis, but it is not believed that this is an essential requirement. The essential requirement is that these conjugates be formed in an area that is rich in macrophages. It is further believed that the conjugate must be of a relatively insoluble character. As a result of stimulation by such an antigen, an antibody is formed that has a cellular affinity, and this constitutes the state of being eczematously sensitized. An eczematous reaction, however, appears only when the simple chemical is brought into contact with the appropriate tissue.

NEUROSYPHILIS

Treatment Using Penicillin Alone and in Combination with Oxophenarsine Hydrochloride and with Bismuth

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ROUTINE examination of spinal fluids of all syphilitic patients admitted to the New Mexico Intensive Treatment Center has been a valuable and productive procedure. The Center opened its doors on Feb. 7, 1944, and during its first two years and three months of operation, a total of 1,722 patients was admitted for intensive treatment of syphilis. Positive reactions of the spinal fluid were discovered in 259 patients (14.5 per cent). The large majority of these patients had never had examinations of spinal fluid before, although many of them had received varying amounts of irregular routine antisyphilitic therapy.

The present report deals with the results which were obtained with penicillin in the treatment of 171 patients, all followed up for periods from three to eighteen months. This number of patients represents 74.0 per cent of the total number who were treated for neurosyphilis with penicillin more than three months before this report and thus were eligible for follow-up examination.

A decision was made to use penicillin in treating these patients as a result of favorable reports in the literature. The initial observations of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council,[1] were encouraging. Follow-up examinations of spinal fluid in 107 patients with neurosyphilis that were studied by the panel showed improvement in 78 patients (slight in 43 and definite in 35), the commonest change being a reduction in the number of cells and in total protein. Symptomatic improvement was noted by such objective means as change in handwriting, encephalographic changes and the disappearance of ptosis and of headache associated with meningitis.

Statistical data prepared by Mary B. Wicker.

1. Stokes, J. H.; Sternberg, T. H.; Schwartz, W. H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B., Jr.: The Action of Penicillin in Late Syphilis Including Neurosyphilis, Benign Late Syphilis and Late Congenital Syphilis: Preliminary Report, J. A. M. A. **126**:73-79 (Sept. 9) 1944.

Subsequent reports have continued this optimistic tone to a greater or lesser degree. Gammon and his associates [2] confirmed the beneficial effect of penicillin on the spinal fluid and noted that improvement began a few days after treatment with penicillin was started and reached a maximum in four months. Better results were obtained with higher dosage than with lower dosage, and best results were obtained with the higher dosage divided into two courses. The experience of Rose and his associates [3] in the treatment of patients with symptomatic neurosyphilis emphasized an immediate increase in cells and in total protein together with a temporary intensification of symptoms. They considered this phenomenon to be a Herxheimer reaction, since it occurred only in previously untreated patients. Subsequent reduction in cells and in protein to normal levels followed by a decrease in the intensity of the Wassermann reaction was likewise noted. Clinical results in 70 patients, followed up from four to twelve months after therapy, were tabulated as 28 patients "improved," 37 "no change" and 5 "worse," with the greatest improvement in patients with dementia paralytica.

Callaway and his associates [4] reported a "favorable therapeutic trend" in the condition of 100 patients with active syphilis of the central nervous system, each treated with a total of 4,000,000 units of penicillin over a ten day period. Sixty per cent of this series of patients showed clinical improvement associated with definite improvement in their spinal fluid, 31 per cent clinical improvement alone, 4 per cent improvement in spinal fluid unassociated with clinical change and 5 per cent clinical deterioration with no improvement or progression in spinal fluid. After therapy negative Wassermann reactions of the spinal fluid developed in 8 per cent of the patients. O'Leary [5] has also noted the prompt improvement in spinal fluids with both objective and subjective clinical improvement. Patients who had meningeal neurosyphilis were most benefited clinically and serologically, while patients who had parenchymatous neurosyphilis were helped only slightly if at all. Peni-

2. Gammon, G. D.; Stokes, J. H.; Beerman, H.; Ingraham, N. R., Jr.; Lentz, J. W.; Horgan, H. G.; Steele, W., and Rose, E. K.: Penicillin in Neurosyphilis: Effect on Blood and Spinal Fluid, J. A. M. A. **128**: 653-654 (June 30) 1945.

3. Rose, A. S.: Penicillin Treatment of Neurosyphilis, Connecticut M. J. **9**:522-525 (July) 1945. Rose, A. S.; Travett, L. D.; Hindle, J. A.; Prout, C., and Solomon, H. C.: Penicillin Treatment of Neurosyphilis: A Preliminary Report of Seventy Cases Followed from Four to Twelve Months, Am. J. Syph., Gonor. & Ven. Dis. **29**:487-493 (Sept.) 1945.

4. Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **30**:110-124 (March) 1946.

5. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, J. A. M. A. **130**:698-700 (March 16) 1946.

cillin given in combination with fever therapy, either with malaria or by means of a fever machine, did not improve the clinical results noted from treatment with fever alone.

A recent thorough evaluation by Stokes and Steiger[6] of results in 283 patients with neurosyphilis who were treated with penicillin at the University of Pennsylvania has confirmed many of the earlier observations. Definite improvement in spinal fluid occurred in 74 per cent of the patients, and normal or near normal spinal fluids were attained in 36 per cent without regard to diagnosis. "Surprisingly little difference" was noted in the response to low dosage schedules compared with response to high dosage schedules. A comparison with older methods, including chemotherapy and fever therapy, indicates that in asymptomatic neurosyphilis treatment with penicillin ranks far above other methods in the degree of improvement, in spinal fluid, but malarial therapy still appears to be better in the production of clinical improvement. All the authors cited concur in the necessity for further observation for at least several more years before conclusive evaluation of the action of penicillin in treatment of patients with neurosyphilis can be accomplished.

MATERIAL

The 171 cases of neurosyphilis in this study were distributed as follows according to diagnosis:

Diagnosis	Number of Cases	Percentage
Asymptomatic neurosyphilis	125	73.1
Meningovascular syphilis	9	5.3
Tabes dorsalis	11	6.4
Dementia paralytica	20	11.7
Optic atrophy	6	3.5

The large majority of patients (73.1 per cent) were entirely asymptomatic, and the remaining patients had relatively mild and early manifestations. As a matter of policy, persons with symptomatic, advanced forms of the disease were not admitted to the Center for treatment. Accordingly, this study may be considered as representing an evaluation of results in the treatment of patients with asymptomatic neurosyphilis and of a small number with the disease in the mild early symptomatic phase. The percentage of male patients was 62.0 and of female patients 38.0. In this series there were 60.2 per cent native Spanish-speaking white persons, 33.3 per cent English-speaking white persons, 1.2 per cent Negroes and 5.3 per cent Indians. There were 11.1 per cent under 20 years of age, 47.4 per cent between 20 and 40 years of age and 41.5 per cent over 40 years of age.

6. Stokes, J. H., and Steiger, H. P.: Penicillin in Neurosyphilis, J. A. M. A. **131**:1-7 (May 4) 1946.

Penicillin alone was used in the treatment of 86 patients (50.3 per cent). The rest of the patients were divided into two groups, each receiving one of two forms of combined penicillin, oxophenarsine hydrochloride with penicillin and bismuth compound with penicillin. The schedules are referred to as the "8-6-3" schedule (40 patients, 23.4 per cent) and the "5-12-3" schedule (45 patients, 26.3 per cent).

The dosage schedule for penicillin alone is 40,000 units administered intramuscularly every three hours for sixty consecutive doses, making a total of 2,400,000 units. This schedule has been used widely for the treatment of early syphilis, especially by the Army and the Navy.

The "8-6-3" schedule, administered during an eight day period, comprises eight daily injections of oxophenarsine hydrochloride (0.06 Gm. for adults weighing more than 120 pounds [54 Kg.] and proportionately less for smaller patients, three injections of bismuth subsalicylate on the first, fifth and eighth days, and penicillin in doses of 10,000 units every three hours for sixty injections, making a total of 600,000 units.

Following the recommendation of the United States Public Health Service that schedule "8-6-3" be discontinued, a modification was employed which is known as the "5-12-3" schedule. During a nine day period, five injections of oxophenarsine hydrochloride are given on the first, third, fifth, seventh and ninth days. Three injections of bismuth subsalicylate, 200 mg. each, are given on the first, fifth and ninth days, and seventy-two injections of 16,667 units of penicillin every three hours are given for a total of 1,200,000 units.

The aforementioned three routines have been used at the Center for the treatment of patients with early or latent syphilis. The employment of these routines in the treatment of asymptomatic neurosyphilis was justified, my colleagues and I felt, by the initial reports of successful therapy with penicillin in neurosyphilis and also on account of the lack of adequate facilities for the administration of fever therapy in the state of New Mexico. Therapy combining penicillin, arsenic and bismuth did not appear to have any justifiable contraindication. The increased therapeutic effectiveness of combining arsenic and bismuth with penicillin has been noted in early syphilis.[7] We felt that the

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7. (*a*) Moore, J. E.; Mahoney, J. E.; Schwartz, W.; Sternberg, T., and Wood, W. B.: The Treatment of Early Syphilis with Penicillin, J. A. M. A. **126**:67-73 (Sept. 9) 1944. (*b*) Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, ibid. **130**:696-698 (March 16) 1946. (*c*) Leavitt, H. M.: The Rapid Treatment of Syphilis: Comparison of Results Using Five Treatment Methods, Am. J. Syph., Gonor. & Ven. Dis., **31**:27-40 (Jan.) 1947. (*d*) Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis. J. Ven. Dis. Inform. **27**:3-9 (Jan.) 1946.

comparison of results of combined therapy with the results of therapy with penicillin alone presented an interesting problem worthy of investigation.

All patients with neurosyphilis were instructed to report for examinations of spinal fluid every three months until told not to do so any more. These patients were also instructed to report for monthly blood tests so that serologic changes could be observed. With few exceptions patients preferred to return to the Center for follow-up examination of spinal fluid, and almost all specimens were sent to the New Mexico State Public Health Laboratory for testing. These circumstances have provided a uniform series of follow-up laboratory reports furnishing the following information: Kolmer's complement fixation test in five dilutions, cell count, colloidal mastic test, Pandy's protein test and quantitative levels of total protein. We have successfully followed up 74.0 per cent of eligible cases for at least three months and most of these for over nine months.

SYMPTOMATIC RESULTS

Evaluation of clinical improvement has not been attempted in this study. Almost all patients (73.1 per cent) were entirely asymptomatic when therapy was initiated, and the remaining patients had symptoms of relatively low intensity. A feeling of general well-being was the rule when patients returned for follow-up examinations. The significance of this type of symptomatic improvement is difficult to determine, since penicillin undoubtedly exerts a beneficial, although perhaps temporary, effect on coincidental sinusitis, bronchitis, arthritis and other ailments associated with low grade infections, in addition to any amelioration of the symptoms of neurosyphilis. We have had no standards for measuring this symptomatic improvement in the neurosyphilis which we have encountered at the Center. Therefore this study will confine itself to objective changes noted in the blood and spinal fluid. It should be noted, however, that several striking examples of clinical deterioration have been observed along with simultaneous improvement in spinal fluid.

STANDARDS FOR EVALUATION OF RESULTS

The results of therapy were studied at three month intervals following treatment. Most patients had varying amounts of irregular routine antisyphilitic therapy before admission to the Center, but none had received fever therapy during the year preceding admission. None of the patients had received any form of rapid treatment for syphilis during the six month period preceding treatment here.

One of the objectives of this study is the demonstration of the effect of a single course of therapy in neurosyphilis. Accordingly,

we have studied the changes in spinal fluid following a single course of treatment for each of the 171 patients. To 35 patients (20.5 per cent) a second course of therapy, not usually the same as the first course, was given because of the appearance, persistence or progression of abnormal laboratory or clinical findings. The more severe the evidence observed, the earlier was retreatment instituted. Results of the second course of therapy have been studied separately.

The following terms were used in comparing follow-up observations of spinal fluid with the original observations preceding treatment: (1) worse, (2) no change, (3) slight improvement (return of cell count or colloidal mastic reaction to normal or clearing in one tube of the complement fixation test), (4) moderate improvement (clearing of two tubes of the complement fixation test or clearing of one tube of the complement fixation test plus return of cell count, colloidal mastic or total protein to normal levels), (5) much improvement (clearing of three tubes of the complement fixation test plus return of cell count, colloidal mastic or total protein to normal levels) and (6) negative (normal results for all tests, a cell count under 10 and levels of total protein under 40 mg. per hundred cubic centimeters).

Another method of demonstrating changes in spinal fluid is classification by groups. This classification, separating spinal fluids into three grades of pathologic changes, has been shown to have some significance in the evaluation of the extent of neurologic damage and the probable outcome in cases of asymptomatic neurosyphilis.

Group 1. Fluids with elevated cell count and/or changes in protein; other aspects normal

Group II. Fluids with changes of moderate intensity in between groups 1 and 3

Group III. Fluids with maximal changes in complement fixation and in colloidal mastic tests (paretic formula)

A third method of evaluating changes in spinal fluid is the classification of each specimen report into "active" and "inactive" groups. An "active" fluid usually connotes a tendency toward progression of the pathologic process and inflammation of meningeal structures. An "inactive" fluid, on the other hand, suggests a quiescent or healing type of neurosyphilis, demonstrating response to therapy and a more favorable prognosis. An elevated cell count (over 10 cells per cubic centimeter) is the usually accepted standard for activity. We considered all levels of total protein over 40 mg. per hundred cubic centimeters of fluid and definitely positive reactions to Pandy's protein test as additional signs of activity. Previous reports have stressed the prompt reduction of activity in neurosyphilis in patients treated with penicillin. We have separated all reports on spinal fluid into active and inactive categories to determine to what degree our own experience bears out these reports.

Regular monthly follow-up blood tests have been studied for all of these patients in order to determine to what extent improvement in the serologic titer parallels changes in the spinal fluid.

RESULTS OF THERAPY

The results of therapy for the 171 patients in this study are presented in tables 1, 2 and 3. For 35 patients who received more than

TABLE 1.—*Changes at Last Examination of Spinal Fluid Following a Single Course of Therapy*

State of Spinal Fluid	Methods of Treatment			
	Penicillin	8-6-8	5-12-8	All Methods
Worse	5	6	2	13
Unchanged	6	8	5	14
Slightly improved	16	3	5	24
Moderately improved	28	7	14	49
Much improved	13	8	7	28
Normal	18 (20.9%)	13 (32.5%)	12 (26.7%)	43 (25.1%)
Total cases	86	40	45	171

one course of treatment the results of the first course only are included. At the last follow-up examination of each of the 171 patients, 24 showed slight improvement, 49 showed moderate improvement, 28 showed much improvement and 43 (25.1 per cent) became entirely normal.

TABLE 2.—*Classification of Spinal Fluid by Groups Before Treatment and at Last Examination Following a Single Course of Therapy*

Method	Group	Number Before Treatment	Number After Treatment
Penicillin alone	Normal	0	18
	I	5	5
	II	62	59
	III	19	4
"8-6-8"	Normal	0	13
	I	0	0
	II	29	25
	III	11	2
"5-12-8"	Normal	0	12
	I	5	4
	II	28	27
	III	12	2
All methods	Normal	0	43
	I	10	9
	II	119	111
	III	42	8

In order to compare each of the three methods of treatment, the term "definite improvement" is used, meaning the total of cases which fall into the groups classified as "moderate improvement," "much improvement" and "entirely normal." Definite improvement was noted in 68.6 per cent of the patients treated by penicillin alone, 70.0 per

cent of the patients treated by the "8-6-3" schedule, and 73.3 per cent of those treated by the "5-12-3" schedule.

It was noted that 20.9 per cent of the patients treated with penicillin alone succeeded in achieving normal spinal fluid, compared with 32.5 per cent for the "8-6-3" schedule and 26.7 per cent for the "5-12-3" schedule.

Spinal fluid became worse in only 13 patients (7.6 per cent). One of these patients had optic atrophy, which rapidly progressed to blindness, seemingly in spite of therapy. The other patients in this small group showed only slight changes for the worse.

TABLE 3.—*Classification of Spinal Fluid by Activity Before Treatment and at Last Examination Following a Single Course of Therapy*

Method	Activity	Number Before Treatment	Number After Treatment
Penicillin alone	Normal	0	18
	Active	50	27
	Inactive	36	41
"8-6-3"	Normal	0	13
	Active	28	11
	Inactive	12	16
"5-12-3"	Normal	0	12
	Active	31	16
	Inactive	14	17
All methods	Normal	0	43
	Active	109	54
	Inactive	62	74
All methods (percentage)	Normal	0	25.1
	Active	63.7	31.6
	Inactive	36.3	43.3

Before therapy 10 patients were in group I, 119 in group II, and 42 in group III. At the last follow-up examination 43 patients were entirely normal, 9 were in group I, 111 in group II, and 8 in group III.

Before therapy the spinal fluid in 109 patients was classified as active and in 62 as inactive. At the last follow-up examination the spinal fluid was active in 54 patients, and in 117 it was inactive or entirely normal.

Thirty-five patients were treated with more than one course of therapy, and the results of the first course are included in the foregoing figures and in tables 1, 2 and 3. A separate analysis of changes in spinal fluid after the second course of therapy shows a tendency toward continued improvement. Three patients showed no change, 4 showed slight improvement, 4 showed moderate improvement and 2 became completely normal. The rest were not available for follow-up examination.

Examination of the blood at monthly intervals failed to show any considerable diminution in titer in almost all of the patients in this

study. Only 8 patients showed a normal titer at the latest follow-up examination. This result is similar to our observations in a study of the response of the serologic titer to the same three schedules of therapy in late latent syphilis.[7c] Of 143 patients with late latent syphilis treated with penicillin alone, the "8-6-3" schedule or the "5-12-3" schedule, only 1 patient succeeded in becoming normal.

COMMENT

Substantial improvement in the spinal fluid was noted in a majority of patients treated by each of the three methods used at the Center. Most of the improvement occurred during the first three month period immediately following treatment. Most rapid improvement was noted in the cell count and in the results of the colloidal mastic test, with changes in the total protein and in the results of the complement fixation test coming later and in lesser degree. These results are entirely in accord with previous reports on the treatment of neurosyphilis with penicillin. These changes are encouraging, but since they represent laboratory observations only, one should be careful not to attribute definite curative powers to penicillin in the treatment of neurosyphilis until adequate follow-up study lasting five years or more has demonstrated the absence of clinical evidence of the disease and also the permanence of the improvement in the spinal fluid.

Careful comparison of the results obtained using each of the three methods, penicillin alone, the "8-6-3" schedule and the "5-12-3" schedule, reveals a higher percentage of improvement in the spinal fluid with therapy combining arsenic, bismuth compound and penicillin. This difference, however, is not statistically significant because of the relatively small number of cases in this study, and it does not appear to be sufficient in degree to warrant exposing the patient to the additional risks of combined therapy. Experience in the treatment of large numbers of patients with early syphilis using the "8-6-3" regimen has disclosed a relatively high incidence of arsenical encephalopathy. It was the frequent occurrence of such conditions during 1945 that caused the United States Public Health Service to recommend the change to the "5-12-3" schedule, reducing the total dosage of arsenic and increasing the penicillin. Thus far, not many serious reactions have been reported as a result of "5-12-3" therapy. We have noted 1 instance of arsenical encephalopathy with this regimen at the Center in treating a patient with secondary syphilis. We do not feel that the added risk of the arsenic, however slight it may be, is justified by the slight difference in improvement in spinal fluid shown in this study by the combined form of therapy over therapy with penicillin alone.

We are of the opinion that a patient with asymptomatic neurosyphilis deserves a trial of at least one course, and probably several courses,

of therapy with penicillin before resort to the severer fever therapy. Many patients suffering from neurosyphilis cannot undergo fever therapy because of debility, complicating constitutional disease, obesity or age. In penicillin we now have a promising form of therapy which can be administered safely and in repeated courses if necessary.

This study has stressed the immediate effect of a course of penicillin therapy with a total dosage of not more than 2,400,000 units. We have been successful in improving the spinal fluid of the large majority of patients treated. Evaluation of the effect of the second course of therapy on spinal fluid is inconclusive because of the small number of patients. Our figures suggest that the tendency toward clearing of the spinal fluid is continued by the second course, but the changes are mostly slight and moderate. The remarkable improvement noted in most patients after the first course of therapy is not seen. We cannot help feeling that, in some instances at least, retreatment has been premature, and that the continued improvement might well be due to the first course of therapy as much as to the second.

A check of the 43 patients whose spinal fluids were normal after a single course of penicillin therapy shows that before therapy 5 of these patients were in group I, 35 in group II, and only 3 in group III. This indicates a better prognosis for patients in groups I and II treated by penicillin and is in accord with the expected results of other forms of therapy, including therapy with arsenicals and fever. Thus, the speed of reversion to complete normality is to some extent a function of the degree of original abnormality.

We have not made an attempt to compare the results of therapy with penicillin with results of therapy with fever, since much more comprehensive study is necessary to shed light on this interesting problem. Follow-up evaluation of change in spinal fluid following malarial therapy cannot be accomplished effectively until two to five years have elapsed. Also, careful selection of comparable cases is needed, since it has been demonstrated that the response to therapy with penicillin in asymptomatic neurosyphilis and in meningovascular syphilis is much more favorable than the same therapy in parenchymatous forms of the disease.

We have not noted serious reactions in these patients as a result of therapy with penicillin. Nevertheless, one should be cautious in commencing treatment of a previously untreated patient, especially when meningeal involvement or cardiovascular damage is suspected, since Herxheimer reactions of serious import have been reported.

SUMMARY

One hundred and seventy-one patients with neurosyphilis, mostly asymptomatic, were treated with a single course of penicillin alone or with a course of penicillin combined with oxophenarsine hydrochloride

and with bismuth. Follow-up examinations of spinal fluid in all these patients showed definite improvement in 69.6 per cent and normality in 25.1 per cent. Most of the improvement occurred in the first three months following therapy, and most rapid improvement was noted in the cell count and in the colloidal mastic test, followed by improvement in the level of total protein. The complement fixation test improved more slowly and to a lesser degree. Improvement in the serologic titer of the blood did not parallel improvement in the spinal fluid. In only 8 patients did the serologic test for syphilis turn normal. Results were slightly better after treatment with combined arsenic, bismuth compound, and penicillin than with penicillin alone. This difference does not appear to be statistically significant, and it is not sufficient to warrant the additional risks of combined therapy as contrasted with the safety of penicillin alone.

Further investigation and study are needed to establish the permanence of improvement in spinal fluid and the absence of clinical relapses following therapy with penicillin in neurosyphilis. Nevertheless, we feel that sufficient evidence is at hand to justify the treatment of asymptomatic neurosyphilis with at least one course, and preferably several courses, of penicillin before resorting to fever therapy.

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SPOROTRICHOSIS

Report of a Case in Which Treatment with Iontophoresis Was Successful

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AND
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DETROIT

THE FOLLOWING case of sporotrichosis is reported since it demonstrates the efficacy of iontophoresis with strong solution of iodine, U. S. P., and the failure of penicillin in the therapy for this disease. While sporotrichosis is usually responsive to treatment with potassium iodide administered orally, an occasional case is encountered in which the disease is resistant to this form of therapy or in which intolerance to large doses of potassium iodide administered by mouth exists.[1] The disease is not a rarity here, yet we have been able to find only 1 other case proved by culture which has been reported from Michigan.[2]

REPORT OF A CASE

W. C., a 72 year old Negro, was first seen in the Dermatology Clinic of City of Detroit Receiving Hospital on March 9, 1945 for treatment of numerous nodular and suppurative lesions of the left hand, forearm and arm of three months' duration.

Past History.—The patient's past history was irrelevant. He was born in North Carolina and had resided continuously in Detroit since 1926.

Present Illness.—The patient cut his left thumb while working in a woodpile during the last week of December 1944. On Jan. 30, 1945 he was admitted to the surgical wards of City of Detroit Receiving Hospital presenting an ulcer at the base of the left thumb, cellulitis of the left hand and forearm, indurated lymphatic channels of the arm and moderate axillary lymphadenopathy. The cellulitis subsided on a regimen of hot magnesium sulfate wet dressings, and he was discharged after four days to be followed through the outpatient department. On February 6 several subcutaneous nodules were noted on the left forearm, and two weeks later ten nodules were counted.

Examination.—On March 9, when he was referred to the Department of Dermatology, the patient presented a series of twenty-six discrete subcutaneous

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1. Ray, L. F., and Rockwood, E. M.: Sporotrichosis: Report of a Case in Which It Was Resistant to Treatment, Arch. Dermat. & Syph. **46**:211 (Aug.) 1942. Loewe, G.: Sporotrichosis of the Cervical Area, J.A.M.A. **107**:1040 (Sept. 26) 1936.

2. Menagh, F. R.: Sporotrichosis: Report of a Case, Arch. Dermat & Syph. **38**:313 (Aug.) 1938.

nodules, beginning at the base of the left thumb, on the dorsal surface, and extending up the flexor aspect of the forearm and the inner surface of the arm to just short of the axilla. These nodules ranged in size from 0.5 cm. to 2.5 cm. in diameter. They were not tender or painful. About half the lesions showed superficial necrosis and exuded a yellowish white, purulent fluid, while the others had not yet reached the suppurative stage. The axillary nodes were not enlarged. There were no constitutional symptoms.

Laboratory Data.—The microscopic and gross characteristics of cultures of purulent material and biopsy tissue grown on Sabouraud's dextrose agar at room temperature were characteristic of Sporotrichum schenki. The organism

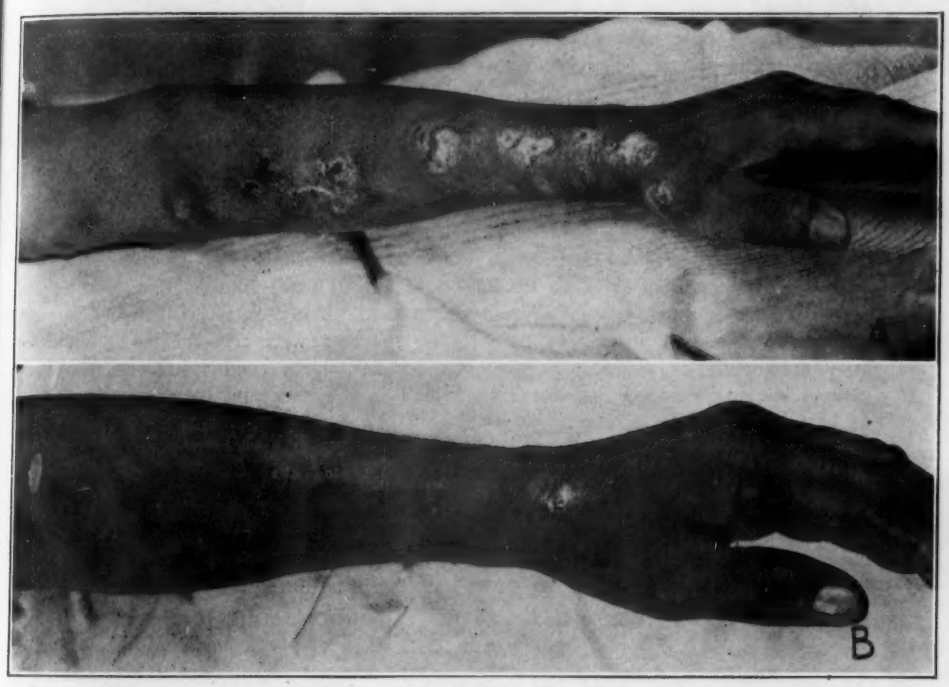

Fig. 1.—*A*, the patient's arm showing lesion of sporotrichosis before treatment; *B*, after eleven weeks of treatment.

was not demonstrated in direct smears. A blood count and examination of urine showed no abnormalities.

Treatment.—The patient was readmitted to Receiving Hospital on March 14 and given a course of sixty intramuscular injections of 20,000 units of penicillin every three hours for a total of 1,200,000 units. No clinical improvement was evident at any time during treatment or four weeks after penicillin therapy, and cultures were still positive for S. schenki.

On April 11 the iontophoretic treatments were begun. These were given daily Monday through Friday for a total of thirteen weeks. Strong solution of iodine, U.S.P., diluted 1 to 100 in isotonic solution of sodium chloride and increased to 1 to 50 after seven weeks was used. Ordinary toweling was moistened in the

solution and wrapped about the arm. Strips of pliable metal were then wound about the toweling spirally. Since the active ion, iodine, is an anion, the negative electrode was attached to the arm, and the large indifferent positive electrode, a moist pad, was placed on the back. For the first two weeks the entire arm was treated in one application, but thereafter separate applications were made to the hand, the forearm and the arm, as the patient was then able to tolerate a greater current to each region. The current was about 15 milliamperes for twenty minutes in the first week, but this was later gradually increased to about 35 milliamperes for thirty minutes to each of the three areas.

After two weeks of such treatment there was striking clinical improvement, although pus could be expressed from a few nodules and cultures were positive. After seven weeks only a few nodules remained, and no suppuration was evident. After eleven weeks all lesions had either been replaced by scar tissue or had healed, leaving only pigmentation, except for a small nonsuppurative nodule at the base of the thumb. Treatment was discontinued. However, two weeks later a few drops of pus were expressed from this remaining lesion, and cultures were again positive. After five days of iontophoretic treatment pustulation had ceased, and after another week of therapy there were no signs of activity. Therapy was then terminated. At no time had the patient received any other local or oral medication. He was last seen six months after termination of therapy and showed no signs of relapse.

Intradermal Test.—An intradermal test was performed five months after complete healing of all lesions with 0.1 cc. of a 1 to 1,000 dilution of a vaccine prepared from cultures obtained from the patient. After forty-eight hours an inflammatory nodule, measuring 25 mm. in diameter with centeral pustulation and surrounding erythema, was present. Similar intradermal injections in 5 control patients produced papules 3 to 5 mm. in diameter and were considered as having elicited no significant reaction.

STREPTOMYCIN

Serial dilutions of Sabouraud's 4 per cent dextrose broth containing concentrations of streptomycin as high as 256 units per cubic centimeter failed to inhibit the growth of S. schenki in inoculations. We therefore feel that streptomycin will be of no value in treating patients with sporotrichosis.

COMMENT

The time-consuming nature and technical difficulties of iontophoresis would not justify its use as the treatment of choice for sporotrichosis. In view of its proved efficacy, potassium iodide administered orally, either alone or in combination with roentgen ray therapy, should be routinely used. However, treatment with iontophoresis may prove to be of value in the occasional case in which the disease does not respond to oral iodides, or in which symptoms of intolerance to large oral doses of iodides may develop. We also feel that in view of the extensive involvement in this case the time required for complete healing of all lesions, thirteen weeks, compares favorably with that required with the usual methods of therapy. In view of the recent work of

Pereyra [3] it is possible that an even more rapid effect could have been achieved had a wetting agent been added to the strong solution of iodine. The failure of treatment with penicillin in this case confirms the earlier experimental work of Keeney and his associates.[4]

SUMMARY

A case of sporotrichosis involving the left upper extremity showed complete healing after thirteen weeks of iontophoretic therapy with strong solution of iodine, U. S. P. There was no improvement after 1,200,000 units of penicillin had been given intramuscularly. In vitro studies demonstrated the failure of streptomycin to inhibit the growth of Sporotrichum schenki. The reaction to an intradermal test with an autogenous vaccine was strongly positive.

Norman F. Conant, Ph.D., Assistant Professor of Bacteriology, Duke University School of Medicine, confirmed the culture as Sporotrichum schenki and prepared the vaccine used in the intradermal tests.

C. W. Buggs, Ph.D., Assistant Professor of Bacteriology, Wayne University College of Medicine, made the in vitro studies with streptomycin.

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3. Pereyra, A. J.: Penetration of Surface Tissues with Copper by Iontophoresis, Arch. Dermat. & Syph. **52**:96 (Aug.) 1945.

4. Keeney, E. L.; Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on Actinomyces Bovis: III. In Vitro Effect of Penicillin, Bull. Johns Hopkins Hosp. **75**:410 (Dec.) 1944.

LUPUS ERYTHEMATOSUS TREATED WITH VASODILATORS AND COLLOIDAL GOLD SULFIDE

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THIS report deals with the results obtained in the treatment of lupus erythematosus with vasodilators and colloidal gold sulfide. Some interesting observations on the relationship of leukopenia, albuminuria and hypertension to the clinical condition of patients were noted.

Kuehnau [1] and Tarentelli [2] were among the early investigators to employ vasodilator therapy in lupus erythematosus. They used the amide of nicotinic acid and reported encouraging results. Recently I reported on the theory and practical use of vasodilators in the management of various dermatoses.[3] Rapid improvement was noted in erythema multiforme and in actinic eruptions. My conclusions were confirmed by Weisberg and Rosen.[4]

For many years I have entertained the idea that anoxia of tissue induced by spasm of the blood vessels prevents gold from reaching the unhealed active lesions of lupus erythematosus. This belief was substantiated by the experiments of Beinhauer, Jacob and Beebe,[5] who found that gold was present in quantities large enough to be demonstrated spectographically in the healed lesions of lupus erythematosus in patients treated with gold sodium thiosulfate, while little if any of the metal was detected in active lesions. This fact probably accounts for the favorable response to treatment reported by Monash

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., June 13, 1946.

From the Northwestern University Medical School and the Outpatient Department of Grant Hospital.

Hille Laboratories, Chicago, supplied a large part of the colloidal gold sulfide used in these studies.

1. Kuehnau, W. W.: Treatment of Lupus Erythematosus with Nicotinic Acid Amide, Klin. Wchnschr. **18**:1117 (Aug. 19) 1939.

2. Tarentelli, E.: Clinical Observation on the Use of Nicotinic Acid in Dermatology, Policlinico (sez. prat.) **48**:61-64 (Jan. 13) 1941.

3. Schmidt, F. R.: Treatment of Dermatoses with Vasodilators, Arch. Dermat. & Syph. **52**:344-346 (Nov.-Dec.) 1945.

4. Weisberg, A., and Rosen, E.: Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **53**:99-106 (Feb.) 1946.

5. Beinhauer, L. G.; Jacob, F. M., and Beebe, P. L.: Spectrographic Analysis of Gold in the Skin Following the Treatment of Lupus Erythematosus, Arch. Dermat. & Syph. **50**:315-319 (Nov.) 1944.

and Traub[6] when gold was deposited directly in the lesions by intracutaneous injections.

A form of gold compound was employed in this investigation that has proved nontoxic even when given in relatively large amounts. This is colloidal gold sulfide, a product containing 86 per cent metallic gold and 14 per cent sulfur in true colloidal form. Each cubic centimeter of the product contains 17.2 mg. of metallic gold. Gold sodium thiosulfate, on the other hand, contains on the average only 3.5 mg. of elemental gold per cubic centimeter of the product. This means that colloidal gold sulfide is much more potent than is indicated by its gold content, because colloids possess a far greater amount of surface energy and catalytic power than do the comparatively weaker crystalline gold salts.

An initial dose of 2 cc. of colloidal gold sulfide is recommended, regardless of whether the intramuscular or the intravenous route is chosen. This is increased to 3 and then to 4 cc. at intervals of four days, after which 5 cc. should be administered every five or six days.

Colloidal gold sulfide may be given not only by the intravenous and by the intramuscular route but also by mouth, an obvious advantage in treating children and persons whose occupation compels them to travel. The oral dosage is still far from being definite, because relatively little colloidal gold sulfide has been given orally. It is suggested that adults take 20 drops three times daily in water or milk after meals. This dosage supplies 150 mg. of metallic gold weekly. Children should take 1 drop three times daily for every 8 pounds (3.6 Kg.) of weight.

To increase the flow of blood to the skin by overcoming vasospasm, 1 tablet of 100 mg. of nicotinic acid is taken after each meal. An additional tablet should be taken fifteen minutes before injection of the gold compound. The amide nicotinic acid does not produce desired flushing of the skin. The dose of nicotinic acid is cut to 50 mg. if the feeling of warmth is uncomfortable. Smoking should be prohibited, because tobacco has an anoxemic effect, similar to the effect of epinephrine, and this tends to neutralize the vasodilating action of nicotinic acid. Exposure to cold and undue physical exertion should be avoided, for they, also, have a vasospastic effect and thus deprive the skin of oxygen.

Throughout the first two years of this study, a watchful eye was kept on the leukocyte count, the sedimentation rate of the erythrocytes, the urine, the blood pressure and particularly the skin for signs of pruritus or of dermatitis. This vigilance was somewhat relaxed after some three hundred and fifty injections had demonstrated that toxic effects from the use of colloidal gold sulfide did not occur.

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6. Monash, S., and Traub, E. F.: Modification Therapy with Gold Compounds in Lupus Erythematosus: Preliminary Communication, Arch. Dermat. & Syph. **24**:110-111 (July) 1931.

Fatigue is a common complaint of women of the childbearing age afflicted with this disease. Frequent rest periods of twenty minutes each during the day are advisable. Anemia due to iron deficiency must be combated with large doses of ferrous sulfate. Dermatologists are prone to overlook the patient's general condition, which is one reason for the ever increasing loss of patients to internists.

An icteric index was obtained in many patients, because Block, Buchanan and Freyberg [7] showed that gold was found in large amounts in the liver of animals receiving colloidal gold sulfide. This is in contrast to the results when a crystalline gold salt, such as gold sodium thiosulfate, was administered, in which case the kidneys contained the larger amounts of gold.

The fate of gold introduced into the blood stream is uncertain. Experiments indicate that colloidal gold is deposited in the liver where it is quickly taken up by the reticuloendothelial cells. This may be its fate in the skin. At any rate, it disappears rapidly from the blood, for concentrations of colloidal gold in the blood plasma are low a short time after intravenous administration of the gold compound.

Thirty patients were treated in this manner; 26 had the chronic discoid type of lupus erythematosus, while the remaining 4 were in the subacute phase. Tabulation of clinical results is omitted from this paper, chiefly because the varied response in individual patients is well known, a tendency to spontaneous involution in some and a tendency to recurrence in others.

A study of these patients reveals that clinical improvement under treatment with colloidal gold sulfide was noticeable in all but 5. Two of the 5 failures occurred in patients exhibiting the subacute type of lupus erythematosus. Four of the patients who improved with this management had previously failed to respond to injections of oxophenarsine hydrochloride, while the majority of the remainder had failed to respond to treatment with a bismuth compound or with gold sodium thiosulfate in varying amounts. The response to treatment bore no relationship to the duration of the disease or to the amount and degree of atrophy. Many of the patients with a history of having had the disease for more than ten years showed clinical arrest in a shorter time than did those who had had it for a relatively brief time. Relapse was observed in 9 patients when chrysotherapy was stopped and either a bismuth compound or liver was substituted.

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7. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: Metabolism Toxicity and Manner of Action of Gold Compounds in the Treatment of Arthritis: Comparative Study of Distribution and Excretion of Gold Following Intramuscular Injection of Five Different Gold Compounds, J. Pharmacol. & Exper. Therap. **73**:200-204 (Oct.) 1941.

In the earlier days of treatment with colloidal gold its use was promptly halted whenever the leukocyte count dropped below 4,000 cells per cubic millimeter. Later a patient with a white blood cell count of 2,400 was given colloidal gold; the leukocyte count rose steadily to 5,000, and the sedimentation rate fell to a normal level. Clinical improvement was rapid. That colloidal gold sulfide seems to possess the added merit of not depressing the leukocyte count has been substantiated in all later cases.

Four persons with hypertension and albuminuria were treated in this series, and no harmful effects were observed. No toxic effects other than the occurrence of mild pruritus in a few patients were encountered. Damage to the liver, as reflected by an altered icteric index, was not detected. Little if any correlation between the clinical picture and the level of the leukocyte count or the sedimentation rate was noted.

The presence of itching in this disease has not been sufficiently emphasized. Fourteen patients complained of itching, and it was interesting to note that patients were usually relieved of this symptom after three or four injections. Of course, the relief from itching may have been due to the action of nicotinic acid.

In 1 patient with lupus erythematosus hypertrophicus et profundus disappearance of the raised border and the cribriform type of atrophy was observed.

The statement of Comroe [8] that colloidal gold preparations are therapeutically less effective in arthritis than are the crystalline salts of gold, probably because of insignificant gold concentrations in the plasma, apparently does not apply to cutaneous therapy. The level of gold in the plasma is obviously not an index of the curative power of gold.

Improvement in patients may be due solely to the change made from one gold compound, such as gold sodium thiosulfate, to another, such as colloidal gold sulfide. This has often been stressed as an explanation for the improvement observed whenever a change of therapy is instituted. However, the improvement noted in my series has been lasting, several patients having remained cured for as long as two and one-half years, so that such an explanation is not applicable here.

I am convinced that one cause of failure in the treatment of erythematous lupus in the past has been a hesitancy to administer large amounts of gold. Large doses must be given, and colloidal gold sulfide is apparently nontoxic even in large doses.

It is also my impression that patients who flush a good deal after taking nicotinic acid show the greatest amount of improvement. The minimal dose for the drug appears to be 100 mg. taken three times daily.

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8. Comroe, B. I.: The Use and Abuse of Gold Therapy in Rheumatoid Arthritis, J. A. M. A. **128**:848-851 (July 21) 1945.

SUMMARY

This report deals with the therapeutic results obtained in 30 patients with lupus erythematosus, chiefly of the chronic discoid type, with the administration of nicotinic acid by mouth and of colloidal gold sulfide intravenously and intramuscularly.

Lasting clinical arrest in this capricious disease is apparently more quickly attained with the combined form of therapy outlined in this report than with former modalities of treatment.

Larger doses of gold than have previously been employed are recommended in the treatment of lupus erythematosus, since the most favorable results were observed in patients receiving relatively large amounts of gold.

The response to treatment appears to be correlated with the degree of peripheral flush induced by nicotinic acid.

These studies further demonstrated that the presence of severe leukopenia, hypertension or albuminuria in persons with lupus erythematosus is no contraindication to treatment with colloidal gold sulfide and vasodilators. It is interesting to note that no correlation could be determined or prognostic deductions made from the level of the white blood cell count, the sedimentation rate of the erythrocytes, the icteric index and the degree of activity of the disease.

No toxic reactions were observed.

122 South Michigan Avenue.

DISCUSSION

DR. LAWRENCE G. BEINHAUER, Pittsburgh: Any therapeutic approach in the treatment of lupus erythematosus is always welcome in a disease in which the therapeutic response has not been uniformly satisfactory. We have been much interested in evaluating the failure of all the lesions of this disease to respond when subjected to gold therapy. We reported at a previous meeting of this association our experiences in determining, by spectrographic means, the distribution of gold in inactive (healed) lesions as well as in the normal skin of patients with this disease receiving gold therapy. We proved to our satisfaction that the presence of gold in the diseased tissues was associated with healing, but we have been unable to determine why gold was always present in the healed lesions and absent in the active lesions.

What mechanism or what barrier existed that prohibited gold from uniformly entering all the diseased tissue is only a matter of conjecture, and only future study will determine this point.

Dr. Schmidt advances the theory that local tissue anoxia, induced by the spasm of the blood vessels, is a reason that gold does not reach the unhealed or the active lesions in this disorder. He suggests the use of a vasodilator, namely, nicotinic acid, as a method of approach, requiring, however, that definite flushing or vasodilatation be present to allow the gold to reach the desired area. This point, we feel, can be approached by the spectrographic examination for gold in these tissues, which may offer substantiation of the theory which he has advanced.

It is interesting to note that the colloidal gold sulfide is nontoxic and can be utilized in relatively higher dosage with safety, and on that basis it warrants future

clinical trial. The decided improvement in the accompanying leukopenia after the use of colloidal gold resembles our similar experience in a few cases in which we have used therapy with promin (sodium p,p'-diaminodiphenylsulfone-N,-N' didextrose sulfonate).

Although one must be cautious in evaluating the curative values of any medication, especially gold, in the treatment of this disease, in the light of our past experience, we feel this mode of therapy advanced by the presenter has definite merit and warrants future consideration in the treatment of this resistant disease.

Dr. Edward A. Oliver, Chicago: We are all confronted with cases of lupus erythematosus that do not respond to our customary treatment with gold sodium thiosulfate, with bismuth or with oxophenarsine hydrochloride. Most of these cases in which Dr. Schmidt has employed colloidal gold sulfide have been of that class. There have been several other cases, such as the cases of subacute disease that he mentioned, that do not fall into this category.

It was with the hope that some method might be devised whereby the gold would more effectively reach the spot that he began this treatment. I have seen and examined practically all these patients, and I can vouch for the statements that Dr. Schmidt has made as to their improvement. Most of them have shown steady but gradual improvement. There have not been any startling results, but I can say that my colleagues at Northwestern and I feel that the method is worth further trial.

Dr. Schmidt has brought out in his paper also the fact that the presence of severe leukopenia, hypertension or albuminuria in patients with lupus erythematosus is no contraindication to treatment with colloidal gold sulfide. That in itself is something that must be considered worth while, because we all know that in treatment with gold sodium thiosulfate we must stop the treatment time and again because of the leukopenia that develops. I still feel that this is only a beginning, and I hope that it will lead to further investigation by Dr. Schmidt. The only objection which I can see to the treatment at all, especially in dispensary work, is the fact that the preparation is not inexpensive; in fact, it is rather expensive. However, we felt that the greater expense of this preparation is worth while. I believe that Dr. Schmidt is going to continue with this treatment, and I wish him further success. I think that he has done a good job so far.

Dr. Anthony C. Cipollaro, New York: Dr. Schmidt is to be congratulated and encouraged for giving to dermatology a new approach to the treatment of diseases—the physiologic approach. The use of vasodilators in the treatment of cutaneous disease is not new. The foreign literature has many articles referring to the use of vasodilators in the treatment of cutaneous diseases that are of dissimilar nature, varying anywhere from urticaria to lupus erythematosus.

Vasodilators are used much more by ophthalmologists, especially in the treatment of blindness due to tobacco, in which spectacular results are obtained if the blindness has not been present too long. The most practical vasodilator is sodium nitrite used intravenously several times a week, and vasodilatation can be maintained with the use of nicotinic acid in doses varying from 25 to 100 mg. three, four or five times a day, depending on the subjective symptoms of the patient. Erythrityl tetranitrate was used prior to nicotinic acid.

I would like to mention also that Dr. Eichenlaub at this meeting made a valuable contribution to this newer physiologic approach to the treatment of diseases and to the causation of cutaneous diseases. Many physicians have had experiences in which pruritic eruptions of various types were connected with some hepatic changes. For instance, I know of a case of a girl 13 years old with a primary carcinoma

of the liver who had a dermatitis-herpetiformis-like eruption which was extremely pruritic. We all know that cinchophen is capable of producing various types of cutaneous disorders, and yet cinchophen is toxic to the liver.

There was another example of a severe pruritic eruption of many years' duration in a patient who had cirrhosis of the liver which was never diagnosed during life. The diagnosis was made at autopsy. Jaundice associated with inflammations and with neoplasms is very pruritic.

The two presentations that we have had at this meeting should stimulate us to do further research in the physiologic aspects of dermatology.

Dr. E. William Abramowitz, New York: We always welcome a new drug or a modification of an old drug to our armamentarium. Gold is gold, and any preparation of it is toxic. The introduction of a new compound of silver was always heralded as safe and claims were made that argyria was not to be feared. These claims failed to materialize.

The use of nicotinic acid in connection with the gold as a vasodilator may prove a valuable addition to the therapy of lupus erythematosus, especially the discoid type. In the Hollander method, with the use of quinine internally and tincture of iodine applied externally, the curative effect was attributed to the action of nascent iodine at the affected site. Perhaps it was not the iodine but the vascular dilatation that developed at the site of the iodine application that accounted for the good results sometimes obtained.

Dr. MacKee has used in some cases of gold-resistant lupus erythematosus of the discoid type mild local applications of solid carbon dioxide to impose vascular dilatation and to encourage increased deposits of the gold compound at the involved areas.

The cardiologists have noticed the favorable effect of nicotinic acid in cardiovascular disease.

I wish to describe a serious reaction from gold that receives only passing mention in the literature. A woman in the early fifties experienced a subacute disseminated type of lupus erythematosus for which she received six or seven injections of 100 mg. of gold sodium thiosulfate intravenously. There was no doubt about the effect of the gold on the cutaneous lesions, but a severe hemorrhagic colitis developed and the patient required hospitalization for two or three months. I was told that several other cases were encountered by gastroenterologists in patients who were being treated for rheumatoid arthritis with various gold preparations.

Dr. Samuel Ayres Jr., Los Angeles: I would like to ask one question. Doesn't the very fact that lupus erythematosus consists of erythematous lesions indicate the presence of vasodilatation in the lesions as they already exist?

Dr. Frederick R. Schmidt, Chicago: I thank the gentlemen who discussed this paper. I certainly am not one to say that this treatment is a cure for this capricious disease, and I heartily subscribe to Dr. Oliver's remark that this modality of treatment has brought improvement in these cases in a shorter length of time than has the older form of treatment in a comparable series of cases, and that is all.

The expense of the treatment is not so great when one considers that this preparation contains 17.2 mg. of gold per cubic centimeter compared with 3.5 mg.

I heartily subscribe to what Dr. Abramowitz said about the toxicity of gold. I merely want to say that this colloidal gold preparation has been used for many years in the treatment of arthritis without any cases of toxicity being reported, so that it is nothing new.

Dr. Ayres brings up an interesting question which I will attempt to answer in a short time. He said that when one looks at a section of lupus erythematosus (at least that is the way I understood the question), vasodilatation is seen in the section; hence it is already there. What one sees is dilatation of the most peripheral blood vessels in the section, the smallest vessels, without seeing the larger arterioles which are constricted. When one considers the work of Lewis and of others, one finds that when histamine is released, it acts as a vasoconstrictor on the arterioles of the skin. In other words, the arterioles are constricted, but the end vessels become dilated. It is a peculiar phenomenon which has been described by Moon and by other pathologists at length. At first a little constriction of the capillaries is seen, but later wide open capillaries are seen as a compensatory result of the previous arteriolar constriction, the whole process ending in tissue anoxia because the circulation is sluggish through the end vessels.

CLINICAL EVALUATION OF UNDECYLENIC ACID AS A FUNGICIDE

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NEW YORK

DURING recent years there have appeared in the literature several reports concerning the fungicidal action of various fatty acids and their salts. The undecylenic acid was discovered to be most effective in laboratory and clinical experiments. Only clinical observations, however, are decisive in evaluating the usefulness of chemical substances in the treatment of fungous diseases of the skin. Laboratory tests in vitro are interesting but not convincing. Often chemicals which give striking results with fungous cultures in test tubes prove entirely useless when applied to human skin.

The observations herein reported were made during the period from October 1944 to January 1946 on patients of the New York University Skin Clinic who were suffering from fungous infections of the skin and nails. Ringworm of the scalp was not included in this investigation.

The diagnosis in all cases was established by microscopic examination of scrapings. Cultures were made only at the beginning of the treatment in order to identify, if possible, the species of fungus involved. Further laboratory controls were made only microscopically. Patients were asked to come to the clinic once a week or once in two weeks. Some, however, did not come regularly. These facts should be taken into consideration in estimating the duration of treatment necessary for a cure.

Two preparations known as "desenex ointment" and "desenex powder" were used. The ointment contains 5 per cent undecylenic acid and 20 per cent zinc undecylenate in a vanishing type base. The powder consists of 2 per cent undecylenic acid and 20 per cent zinc undecylenate in talc.[1] The patients were instructed to rub the ointment into the affected parts of the skin and then to dust with the powder. This procedure was repeated twice daily. The area was washed with soap and water once or twice daily. In cases of fungous

From the Department of Dermatology and Syphilology of the New York University College of Medicine on the service of Dr. Frank C. Combes.

1. The preparations used in this investigation were supplied by the Research Department of Wallace and Tiernan Products, Inc., Belleville, N. J.

infections of the feet the patients were advised to dust the powder into their socks, or stockings, and shoes. Men were asked to change their socks daily and to disinfect them by boiling in soap and water for fifteen minutes. Women were advised to wear pads of cotton cloth covering their feet under their stockings. The pads were changed daily and disinfected by boiling. This precaution is useful because women's stockings made of silk, rayon or nylon cannot stand boiling. Patients with fungous involvement of the nails were instructed to scrape the nails thoroughly daily and then to rub in the ointment.

Several patients who had started the treatment and had discontinued it after the first or the second visit to the clinic were not included in this study. There remained 39 patients worthy of discussion. Thirty-four of them were analyzed as clinical entities. Five others presented combinations of fungous lesions with different localization and possibly different response to therapy; for instance, dermatophytosis and onychomycosis. These conditions were considered separate clinical entities, so that 39 patients presented 44 cases of mycosis for analysis.

The results of treatment were divided into (1) cure, (2) doubtful result and (3) failure. A patient was considered cured if a microscopic examination revealed no fungi and the skin became clinically normal. In some cases of dermatophytosis of the feet, however, it was impossible to bring the skin to an absolutely normal condition. Slight scaling or maceration, especially in the toe webs, persisted, even though microscopic examination did not reveal fungi. Such patients were also regarded as cured. The date of the first microscopic examination in which fungi were not seen was accepted as the date when the cure had been achieved, provided that there were no clinical or laboratory relapses. The result of the treatment was considered doubtful in spite of the microscopic examination if the clinical changes persisted to a considerable degree. The treatment was considered a failure if fungi were seen in microscopic examination regardless of the clinical improvement.

Table 1 gives a summary of all cases in regard to the clinical form, results of laboratory examination and results of treatment.

DERMATOPHYTOSIS OF THE FEET

Of 28 patients with dermatophytosis of the feet, 18 were registered as cured, 5 as doubtful and 5 as failures. Four patients were considered cured after a single microscopic examination did not reveal fungi. All these patients presented lesions on the soles. The infection in 3 patients cleared completely. The fourth patient showed a few scales when last seen, but the scales were free from fungi microscopically. Ten of the cured patients had two microscopic examinations in which fungi were absent. In 5 slight scaling of the toes was still noticeable.

Four of the cured patients had three microscopic examinations showing absence of fungi, and in 2 of them some scaling and maceration persisted.

A microscopic examination showing freedom from fungi is especially significant if it is obtained after the treatment has been discontinued. In 6 out of 18 cured patients the microscopic examination showed freedom from fungi from two to five weeks after the treatment had been stopped. In all 18 cured patients there were no microscopic relapses. When the microscopic examination showed absence of fungi, it continued to do so if repeated a second and a third time.

TABLE 1.—*Clinical Form of Dermatomycosis, Laboratory Data and the Results of Treatment*

Diagnosis	Laboratory Results	Number of Cases	Results of Treatment		
			Cure	Doubtful	Failure
Dermatophytosis of feet	T. interdigitale	8	5	1	2
	T. purpureum	2	..	1	1
	E. inguinale	1	1	..	..
	Monilia (microscopically only) and T. interdigitale	1	..	..	1
	Microscopic evidence of ringworm type only	16	12	3	1
	Total of dermatophytosis of feet	28	18	5	5
Dermatophytosis of hand	Microscopic evidence of ringworm type only	1	1	..	..
Generalized dermatomycosis	T. purpureum and E. inguinale	1	1	..	..
	Microscopic evidence of ringworm type only	1	1	..	..
Tinea cruris	Microscopic evidence of ringworm type only	1	1	..	..
Onychomycosis	Microscopic evidence of ringworm type only	2	1	1	..
	Microscopic evidence of ringworm and monilial types mixed	2	..	..	2
Moniliasis	Monilia albicans microscopically and in cultures	2	..	..	2
Pityriasis versicolor	Microscopic evidence only	6	4	..	2
Total of all cases		44	27	6	11

Table 2 shows the duration of treatment required for cure in patients with dermatophytosis of the feet. Since the patients were coming to the clinic at intervals of one to two weeks, the periods of time given in the table should be regarded as maximum. The actual cure could have taken place somewhat earlier than indicated.

This table shows that the patients in all cases except 1 were cured in two to seven weeks. The last patient was registered as cured after fourteen weeks of treatment only because he failed to come to the clinic for two months.

Cultures were successful in only 6 out of 18 cured patients. Trichophyton interdigitale was grown from 5 patients who were cured in four to seven weeks. Epidermophyton inguinale was obtained from 1 patient who was cured in two weeks.

In 5 patients with dermatophytosis of the feet, the result of treatment was considered doubtful. All these patients were free of fungi on one microscopic examination. They were not registered as cured, however, because the clinical changes still persisted when the patients were seen for the last time. The period of observation was from two to eight weeks. From 1 patient T. interdigitale was cultured and from the other patient Trichophyton purpureum.

In 5 patients the treatment failed to eradicate the infection. One of these patients showed fungi microscopically after two weeks of treatment but failed to return to the clinic. Two other patients, in 1 of whom the infection was due to T. interdigitale and in the other to T. purpureum, showed fungi in scrapings after three and one-half months of treatment. One of these 2 patients was not treated regularly. The fourth patient, who was infected with T. interdigitale, treated himself for six weeks, then discontinued treatment and came to the clinic two months later when fungi were seen microscopically. This

TABLE 2.—*Duration of Treatment Required for Cure of Dermatophytosis of the Feet*

Number of Weeks	Number of Cases
2	4
4	6
5	4
6	1
7	2
14	1

could possibly be a reinfection. The fifth patient had dermatophytosis of the toes and onychomcosis of the toe nails. Microscopic examination of the toe nails revealed a mixed infection with fungi of the ringworm type and the genus of Monilia. The toes on first examination showed only ringworm type of parasites. They cleared up and became microscopically free from fungi after three weeks of treatment. Four months later the toes were again infected. Fungi were observed microscopically and were eradicated after one month of treatment. Five months later the toes were reinfected, this time with Monilia fungi. In this case the treatment of dermatophytosis failed obviously because of repeated reinfection, first with ringworm fungi and later with fungi of the genus of Monilia, the reservoir of both parasites being present in the toe nails. Culturally only T. interdigitale was seen in the toes at the beginning of observation. Cultures from the nails were negative.

DERMATOPHYTOSIS OF THE HAND

Only 1 case of a true fungous infection of the hand (not an allergic eruption) was observed in a patient who also had dermatophytosis of the toes. The patient was cured of both in five weeks.

TINEA CRURIS

One case of tinea cruris was treated. Itching disappeared in a few days, and the patient was cured both clinically and microscopically in eleven days.

GENERAL DERMATOMYCOSIS

The first patient with generalized dermatomycosis was a woman with involvement of the toes, thighs and buttocks. Fungi of ringworm type were observed microscopically in all affected parts. The itching disappeared on the second day after the beginning of the treatment. Three weeks later the skin was almost completely clear, and the scrapings were free from fungi. Two months later the patient informed the clinic by telephone that her skin was "perfectly normal." This patient was considered cured.

The second patient was a man with lesions on toes, soles, groin and buttocks. Some of his toe nails and finger nails were also affected. All these parts showed ringworm fungi on microscopic examination. Cultural observations were of unusual interest. The groin showed E. inguinale, the soles showed T. purpureum and the toes both these parasites together. Cultures from the buttocks and nails failed. The treatment was successful as far as the skin was concerned. Toes and groin were cured in four weeks and soles in six weeks. The lesions on the buttocks were more resistant and required three and one-half months of treatment. It is noteworthy that T. purpureum, a resistant species, was cultured from the toes and the soles. Both cleared up clinically and were twice observed to be microscopically free from fungi.

GENERAL REVIEW OF RINGWORM INFECTIONS OF GLABROUS SKIN

Duration of the Disease.—The duration of the disease had no influence on the duration of treatment necessary for a cure. The history given by the patient is usually unreliable. The patient may fail to notice the changes in the toe webs for a long time or he may call "ringworm" or "athlete's foot" a condition which was not of fungous causation. It can be pointed out, however, that 1 patient with a history of having had the infection for only one month required six weeks of treatment while other patients with histories of having had the infection up to fifteen years were cured in two weeks.

Clinical Type of Lesions.—The clinical type of the lesions, whether erythematous, squamous, intertriginous, fissured, vesicular or bullous, had no influence on the result of therapy. It should be noted also that there were no cases of the distinctly hyperkeratotic type, which is considered more resistant to treatment.

Effect of Undecylenic Acid on Itching.—The effect of undecylenic acid on itching was, in general, good. One patient stated that itching disappeared on the second day after the beginning of the treatment.

Several patients noted relief from itching in a few days or one week. In some cases, however, itching persisted for five weeks.

Resistance of Fungi to Treatment.—On the basis of repeated microscopic examinations it can be said that fungi are capable of surviving a rather long period of treatment with undecylenic acid. In 3 of the cured patients fungi were still present in the scrapings after three weeks of treatment and in 1 other patient after six weeks. In 3 patients for whom the treatment failed fungi were seen microscopically three and one-half months after the beginning of the observation.

ONYCHOMYCOSIS

Of 4 cases of onychomycosis toe nails alone were involved in 3 cases, and toe nails and finger nails in 1 case. In 1 case, only one toe nail was affected. Fungi of the ringworm type were observed microscopically. This nail cleared up clinically and was twice observed to be microscopically clear, with a two month interval between the examinations. The first microscopic examination which did not reveal fungi was obtained six weeks after the beginning of the treatment. Such success in a case of onychomycosis, which is usually resistant to any therapy, was probably due to a rather superficial involvement of the nail plate.

In the second case of onychomycosis of one toe nail fungi were still observed microscopically three and one-half months after the beginning of the treatment. Six weeks later, however, fungi were absent on microscopic examination. The new growing nail looked much improved but not quite normal. The result of treatment in this case was considered doubtful.

In the 2 last-mentioned cases of onychomycosis the microscopic examination revealed the presence of a mixed infection with fungi of the ringworm type and of the genus of Monilia. In both cases the treatment failed. In 1 patient fungi were still present three months and in the other six months after the beginning of the treatment. Cultures were unsuccessful in all 4 cases of involvement of the nails.

MONILIASIS OF THE SKIN

In 2 patients fungi of the genus Monilia were observed microscopically and culturally. One patient with interdigital erosions on both hands was treated for four months. Her cutaneous lesions, although of a superficial type, showed no clinical improvement, and the scrapings continued to show fungi microscopically. The second patient with a paronychia of several fingers did not improve after five weeks of treatment. The microscopic examination was not repeated. In both cases the treatment was considered a failure.

PITYRIASIS VERSICOLOR

Of 6 patients with pityriasis versicolor, 3 were cured both clinically and microscopically in from one to four weeks. The fourth case cleared clinically after two and one-half weeks of treatment. It was registered as cured although the patient did not come for a microscopic examination. The fifth patient was not cured after ten days of treatment as determined clinically and microscopically. The sixth case of pityriasis versicolor was unusually resistant. Repeated clinical and microscopic relapses were observed. The patient presented visible lesions and fungi were observed microscopically after four months of treatment.

None of the 44 patients with various fungous diseases who were treated with preparations containing undecylenic acid showed any objective or subjective evidence of cutaneous irritation due to this chemical substance. If one takes into consideration that some patients presented acute inflammatory vesicular and bullous lesions for which the old reliable fungicidal chemicals such as salicylic acid and sulfur were contraindicated because of the possibility of dermatitis venenata, the importance of the lack of evidence of cutaneous irritation becomes obvious.

SUMMARY AND CONCLUSIONS

Two new preparations ("desenex"), an ointment containing 5 per cent undecylenic acid and 20 per cent zinc undecylenate and a powder containing 2 per cent of the same acid and 20 per cent of its zinc salt, were used for treatment of various fungous diseases of the skin, which were proved microscopically and, in part, culturally.

Forty-four patients who were treated with undecylenic acid presented the following clinical forms: dermatophytosis of the feet (28), of the hand (1), generalized (2), tinea cruris (1), onychomycosis (4), moniliasis (2) and pityriasis versicolor (6). The patient was considered cured when the skin became clinically normal and microscopically free from fungi. In some patients with slight remaining cutaneous changes a microscopic examination showing absence of fungi was considered sufficient proof that a cure had been achieved.

Of 32 patients with dermatophytosis of varied localization and tinea cruris, 22 (68.7 per cent) were cured, the results for 5 remained doubtful and in 5 the treatment failed. The cure required from eleven days to three and one-half months, the average time being thirty-five days. The duration of the disease and the clinical type of the lesions had no influence on the duration of the treatment necessary for cure. In some cases fungi could be observed microscopically several weeks and even three and one-half months after the beginning of the treatment. The number of positive cultures was too small for definite conclusions. It can be noted, however, that 5 of 8 patients with infection due to Trichophyton interdigitale were cured, as were 2 patients with infection

due to Epidermophyton inguinale while only 1 of 3 in whom the infection was due to Trichophyton purpureum was cured. Onychomycosis proved as resistant to undecylenic acid as to other chemicals. Only 1 patient of 4 was cured. In 2 patients with moniliasis (paronychia and interdigital erosions) the treatment failed. Pityriasis versicolor proved rather resistant to treatment. Four of 6 patients were cured in one to four weeks.

Undecylenic acid did not irritate the skin even in patients with acute vesicular and bullous eruptions. In fungicidal effect undecylenic acid was in general satisfactory but not superior to other chemicals used in the treatment of mycoses. However, the combination of a considerable fungicidal effect with a lack of irritation makes undecylenic acid valuable, especially in cases of acute inflammatory fungous eruptions and for patients with sensitive skins.

55 West Forty-Second Street.

EXTRAGENITAL CHANCRE OF THE EAR

ANTHONY S. RIPA, M.D.*
EAST BOSTON, MASS.
AND
LIEUTENANT COLONEL ALEXANDER G. BARTLETT
MEDICAL CORPS, ARMY OF THE UNITED STATES

EXTRAGENITAL chancres may be found on any portion of the body, and a case is being reported to further support this statement.

The standard textbooks on syphilis, as well as the available literature, have been carefully searched, and no mention is made of a primary chancre of the ear. In a survey of 68 cases of extragenital chancres over a twenty-five year period at the University of Michigan by Wile and Holman,[1] extragenital chancre of the ear is not mentioned.

The case herein presented illustrates the important reality that any unusual lesion can be due to syphilis. This is often overlooked and is probably one of the reasons for the many unexplained positive Wassermann reactions found in routine examinations. With the advent of penicillin it is certainly more important now than it was before to diagnose and treat these lesions as quickly as possible. Every day lost results in a wider dissemination of the spirochete and less chance of an early and permanent cure.

REPORT OF A CASE

A 25 year old private was admitted to the Army Service Force Regional Station Hospital on June 11, 1945, complaining of a painless lesion in the right ear of two weeks' duration. The lesion started as a small blister, which broke down to form an ulcer. This ulcer first appeared on the right external canal on the concha, but it gradually became larger and spread inward, involving the entire canal. The patient was given local treatment as an outpatient by the eye, ear, nose and throat service for ten days, with no improvement.

From June 11 to 29, the patient was treated in the hospital with local application of several medicaments (20 per cent silver nitrate, sulfathiazole ointment, 2 per cent gentian violet medicinal and boric acid powder). Despite all this treatment, the lesion did not improve. A biopsy was performed on June 27. On June 29 the patient was examined by the dermatologic and venereal disease sections, at which time examination revealed a large, secondarily infected ulcer in the

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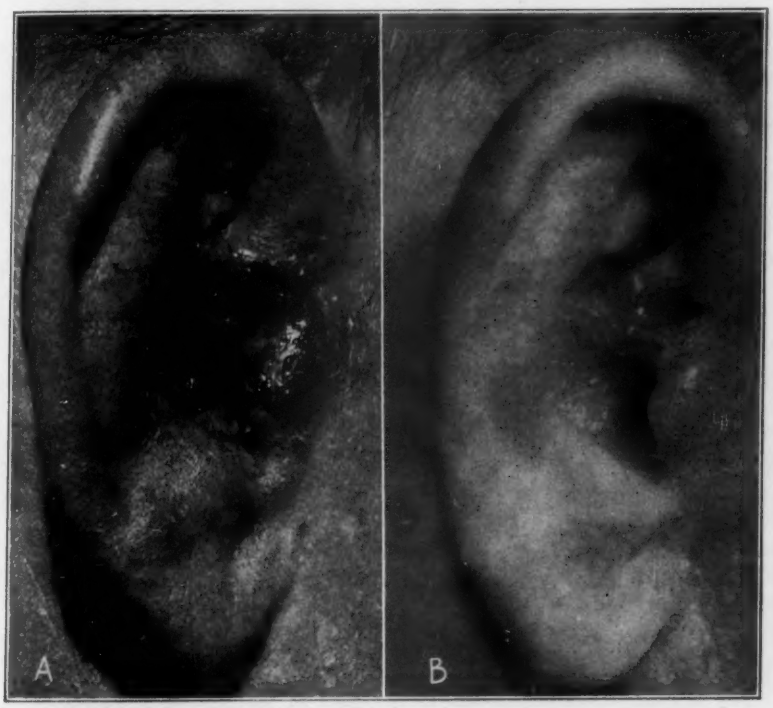
* Formerly Lieutenant, Medical Corps, Army of the United States.

From the Medical Service, Army Service Force Regional Station Hospital, Fort Ord, Calif.

1. Wile, U. J., and Holman, H. H.: A Survey of Sixty-Eight Cases of extragenital Chancres, Am. J. Syph., Gonor. & Ven. Dis. **25**: 58-66 (Jan.) 1941.

external canal of the right ear (figure, *A*). The surrounding tissue was swollen, red and indurated. Unilateral lymphadenopathy was present on the right side of the neck and below the right ear lobe. A fine macular rash was noted on the chest and back. Dark field examinations were performed on several occasions, and they revealed numerous Treponema pallidum organisms per field. Serologic tests for syphilis revealed a positive Kahn reaction with 20 Kahn units and a positive Wassermann reaction. Several serologic tests of the blood were performed, all of which gave strongly positive reactions.

The lesion of the ear was not typical of a chancre, because it had been distorted by previous removal of a biopsy specimen and because it was secondarily infected. However, it had a granulomatous base.



A, chancre of the ear. *B,* chancre after four days of treatment with 2,400,000 units of penicillin.

A diagnosis of a primary chancre of the ear was made because of the following factors: (1) history of several exposures to "pick-ups" during the latter part of April and the early part of May 1945; (2) previous negative serologic reactions of the blood for syphilis; (3) dark field examinations positive for Treponema pallidum on several occasions; (4) repeated positive Wassermann and Kahn reactions (a quantitative Kahn test gave a positive reaction with 20 units), and, (5) a macular rash on the chest and back.

Treatment.—The patient was given intensive penicillin therapy, consisting of sixty consecutive intramuscular injections of 40,000 units each at three hour intervals, for a total dose of 2,400,000 units. He had both a focal and a systemic

Herxheimer reaction during the first day of treatment. The focal reaction consisted of an aggravation of the primary lesion. The ulcer and entire ear became swollen and painful. Further enlargement of the local lymph nodes was noted. The secondary macular rash became brighter in color. The systemic reaction was characterized by chills and fever, the temperature reaching a peak of 103.4 F. The fever subsided in twenty-four hours, and then the temperature remained normal. The ulcer became free of exudate on the third day of treatment, and the cervical lymph nodes became normal on the fourth day of treatment. The entire lesion cleared up completely two days after completion of penicillin therapy (figure, *B*).

Clinical Notes

TRICHONODOSIS
Report of a Case

A. G. PRATT, M.D., CAMDEN, N. J.

Trichonodosis, or knotted hair, is described briefly by McCarthy.[1] He mentions two types. One variety, rarely seen, occurs as a solitary knot associated with abnormal growth of the hair. The second type is commoner, according to the European authors [2] cited by McCarthy. This variety occurs as multiple knots and probably results from physical and mechanical forces such as combing, singeing, washing and the habit of running the fingers through the hair.

McCarthy stated in 1940 that there are no reports of this condition in the American literature. The "Quarterly Cumulative Index Medicus" for the years 1939 to 1945, inclusive, contains no American references and only one foreign reference.[3] The index of *The Journal of the American Medical Association* for 1946 and the index of the *Current List of Medical Literature of the Army Medical Library* for 1946 contain no references to trichonodosis.

In addition to McCarthy's chapter the subject is mentioned in the texts of other American authors [4] on the basis of the European articles. The Suttons illustrate their article with a photograph of multiple knotted hairs supplied by F. Ronchese of Providence, R. I.

The following report deals with the solitary knot type of trichonodosis.

REPORT OF A CASE

J. DiN., a 25 year old woman of Italian parentage, was first seen Nov. 1, 1945 because of loss of hair of three years' duration. The loss started gradually and was continuous.

The scalp was clean, though with a small amount of loose white scale. The most prominent feature of the scalp was the diffuse partial alopecia at the frontal area and at the vertex. Here the remaining hairs were dry, dull appearing and short, varying from 2 to 10 cm. in length. The hairs in the parietal and occipital areas of the scalp were longer, up to 20 cm. in length, but likewise dull and dry.

1. McCarthy, L.: Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, pp. 103-104.

2. Westphalen, V.: Ueber einige Haarerkrankungen, Leipzig, J. A. Barth, 1884, vol. 19.
Kren, O.: Ueber das Vorkommen der Trichonodosis, Wien. klin. Wchnschr. **20**:916, 1907.

3. Cajkovac, S.: Morphology and Pathogenesis of Trichonodosis, Liječn. vjes. **61**:471, 1939.

4. Pusey, W. A.: Principles and Practice of Dermatology, New York, D. Appleton & Company, 1911, p. 986. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1943, pp. 1248-1249. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939, p. 1312.

On close examination it was observed that the ends of most of the hairs were broken, showing trichorrhexis and trichoptilosis. One hair appeared to have a small node near the free end. This hair when viewed microscopically was seen to contain the knot shown in the illustration.

The patient was partially deaf and had a cleft palate. No other abnormalities were revealed in physical examination. There was no loss of hair or other abnormality except as described on the scalp. The blood count was normal and the Wassermann reaction was negative.

From November 1945 to the time of writing the patient has used a tonic lotion on the scalp and has had supportive treatment with vitamins. The most recent examination (January 1947) showed a scalp free from scale, considerable regrowth of hair, no trichorrhexis and only a few hairs with longitudinal splitting. Repeated search has failed to show any more knotted hairs.

Trichonodosis of hair.

SUMMARY

A case of solitary type of trichonodosis associated with trichorrhexis, trichoptilosis and partial alopecia is reported.

516 Cooper Street.

CUTANEOUS PUNCH

HERMAN GOODMAN, M.D., NEW YORK

Reexamining the files of the *Journal of Cutaneous and Genito-Urinary Diseases* disclosed the following correspondence between Dr. B. A. Watson and Dr. E. L. Keyes in July 1887:

"Dear Doctor: Having seen your article in the March number of the *Journal of Cutaneous and Genito-Urinary Diseases* on the subject of the "Cutaneous Punch," I wish to call your attention to the fact that an instrument for the same purpose and of similar construction was used by me in 1877 and was fully described in two articles published, one in the *New York Medical Record*, July 27, 1878, page 78, entitled "Discotome" and the other in the *St. Louis Medical and Surgical Journal*, Vol. XXXV, page 145, entitled 'Gunpowder Disfigurements.'

"Yours sincerely,

"B. A. Watson."

"To the Editor of the Journal of Cutaneous and Genito-Urinary Diseases:—"Dear Doctor: I am entirely unconscious of ever having seen either of the articles referred to above, but it is only just to Dr. Watson that he should have the credit of priority if he wishes it, and the publication in your Journal of this letter with mine will give it to him.

"Yours very truly,

"E. L. Keyes."

Is it not curious, though, that sixty years later the punch is almost always referred to as the Keyes punch?

18 East Eighty-Ninth Street.

CAUTERY DRAINAGE OF SUBUNGUAL ABSCESS

THOMAS S. SAUNDERS, M.D., PORTLAND, ORE.

Collections of pus under the nail plate can be satisfactorily opened and drained, without anesthesia, by applying a small heated cautery tip [1] to the portion of the nail overlying the pus. In an instant, a small opening is formed and the pus escapes. The immediate relief of pain is gratifying.

This procedure is a modification of that used by a colleague, Dr. R. E. L. Holt, for the treatment of subungual hematoma. He heats a small wire (piece of paper clip) to white heat and burns an opening in the nail plate, releasing the blood.

In some instances cautery drainage of subungual abscess will not suffice. Cure will be obtained in such cases only by removal of a portion of or the entire nail.

1020 Southwest Taylor Street.

1. Number 3 cautery tip, National Electric Instrument Co., Long Island, N. Y.

Editorials

PROPOSED DERMATOLOGIC FOUNDATION

The late Bruno Bloch, after a six weeks' trip in the United States in 1928, was asked to write his impressions of American dermatology. He was much interested by what he saw in the various centers visited and commented favorably on the variety and content of the scientific papers that he heard delivered at our national meetings. He pointed out that the educational level and the achievements of the men he met compared favorably with those of his European colleagues, but he deplored the position of dermatology in our medical schools. He emphasized that in this large country with its many excellent medical schools our departments of dermatology did not compare well with the majority in Europe.

If the accomplishments of American dermatology over the past fifty years are critically reviewed, it becomes apparent that they have been attained by the zeal, enthusiasm and hard work of individual dermatologists, while our official status in American medicine has not proportionately advanced.

In every dermatologic center in America, the leaders have been successful practitioners who have devoted a portion of their time to teaching and to purely scientific pursuits. Their private success made it possible for them to visit foreign centers, to attend meetings, to contribute financially to their departments and, at the same time, to advance their personal knowledge. They had the ability to conduct good undergraduate courses. When graduate instruction ceased in Europe because of the wars and young American physicians desiring to specialize in dermatology sought instruction at home, the need for more and better organized departments became apparent. At many schools a valiant effort has been made to furnish adequate instruction, but lack of facilities, such as hospital beds, sufficient numbers of well trained staff men and an adequate budget discouraged and prevented the establishment of departments measuring up to the level that the position of the leaders in the specialty warranted.

American dermatology can no longer rest or be carried along on the laurels and efforts of its leaders alone. The medical schools must realize that what has been accomplished has been by the almost superhuman efforts of individuals, and they must be made to realize that dermatology deserves more and better support.

We are not the only specialty that has outgrown its official position. The American Psychiatric Association, at their recent meeting in New

York, established a foundation the purpose of which is to assist medical schools in improving the undergraduate and graduate instruction in psychiatry. The association proposes to assist in the selection of teachers when vacancies occur, to outline an adequate curriculum in the teaching of mental diseases and to offer advice in general to the medical schools on all subjects pertaining to psychiatry.

The specialty of dermatology also needs such a foundation. The important representative societies must sponsor such a movement. We must be the aggressors in securing for dermatology a better position in our schools and in the medical departments of the armed forces.

The passing generation of practitioner teachers need the help of and eventually will be supplanted by selected young men who are trained and suited for and willing to elect an academic career in dermatology. The medical faculties must furnish them with the material with which they may teach, do fundamental research and thus advance our knowledge of cutaneous medicine.

It is urged that the officers of our various societies consider the establishment of a dermatologic foundation, and it is earnestly hoped that in this endeavor they will receive the support of all dermatologists and medical faculties in securing for the specialty the facilities and the place in our system of medical education which its attainments and its future deserve.

Current Comment

ANNUAL MEETINGS

The annual meetings of the American Dermatological Association, Inc., the Society for Investigative Dermatology and the Section on Dermatology and Syphilology of the American Medical Association held June 1947 were notable events in many respects. They were unusually well attended, and the papers, which in general indicated careful preparation, were practical and interesting and stimulated thoughtful discussions. The subjects were extensive and diversified and included almost all aspects of dermatology. There were discussions devoted to the newer field of geriatric dermatoses, cutaneous reactions to systemic disease, new drugs, new treatments for familiar diseases, new laboratory investigations, problems of nosology and even problems of training in dermatology. The advisability of holding an international congress of dermatologists in the near future was also discussed informally.

Dermatology participated actively in the eminently successful centenial celebration of the American Medical Association. The achieve-

ments of the past century in dermatology were reviewed by Dr. Ormsby, and Dr. O'Leary told the story of syphilis during the past one hundred years. The international outlook in dermatology was pictured in an inspiring address by Dr. R. M. B. MacKenna of Great Britain, a guest of honor of the Section on Dermatology and Syphilology of the American Medical Association.

Dermatology in this country is doing well. It is lusty, it is thriving and it is healthy—and that is particularly gratifying because it has grown from within. No longer is it born of European training. Our own centers are now turning out a constant stream of young men trained both in the basic sciences relating to the specialty and as expert practitioners. As the old practice of apprenticeship training continues to expand, we may confidently foresee the time when the entire country will benefit from the services of well trained, capable dermatologists. The situation will then approach the ideal when more men will devote full time to the study and investigation of the fundamental sciences related to dermatology.

Society Transactions

MANHATTAN DERMATOLOGIC SOCIETY

E. W. Abramowitz, M.D., *President*

Wilbert Sachs, M.D., *Secretary*

Nov. 13, 1945

Erythema Annulare Centrifugum. Presented by Dr. Jack Wolf.

E. H., a man aged 53, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with an eruption on the back and abdomen of five months' duration. He gives no history of ingestion of drugs.

The lesions are of gyrate, circinate and annular configuration, ranging from 5 to 10 cm. in diameter. The borders of the lesions are raised, pink, firm and smooth; the centers are clear.

The eruption has improved somewhat with weekly injections of bismuth subsalicylate.

DISCUSSION

Dr. David Bloom: The lesions are not annular but serpiginous, and some are circinate. Bismuth therapy is indicated in these cases.

Dr. Eugene F. Traub (by invitation): While I have seen improvement with injections of a bismuth preparation, the results do not compare with those of irradiation with small doses of cold quartz–mercury vapor light. Not infrequently one treatment will result in the disappearance of a fixed patch of erythema which has been present for months or years. Unfortunately, the eruption has a tendency to return, so that the combination of bismuth therapy and cold quartz–mercury vapor irradiation is better than either alone. Why the eruption should disappear so promptly after exposure to the cold quartz–mercury vapor radiation I do not know.

Dr. Samuel M. Peck: I get the impression that this disorder is unusually prevalent. I have never seen so many cases at one time, both in hospital and in private practice. It is almost like an epidemic.

Dr. George C. Andrews: I agree that this disease is unusually prevalent. I have 2 patients now under my care, more than I have had in years. I wonder whether any one has tried the sulfonamide drugs or penicillin in the treatment of this disease.

Dr. Mihran B. Parounagian: I suggest that the kidneys be thoroughly examined. I recall a case at Bellevue Hospital, that of a man who had somewhat more pronounced lesions, with elevated borders; the eruption looked like erythema multiforme. He died of a renal disease, and autopsy showed that the kidneys were full of pus. I believe the kidneys were the cause of the cutaneous eruption.

Dr. George C. Andrews: In the literature many varieties are described.

Dr. David Bloom: The variety of erythema annulare centrifugum described by Lipschütz differs from that described by Darier chiefly in the number of lesions. There is no essential difference between these two types.

Dr. E. W. Abramowitz: Although the case is fairly typical, there should be an examination for fungi. I have been surprised at the response of this eruption to injections of bismuth subsalicylate. The eruption returns, however, and the treatment has to be repeated.

Dr. Jack Wolf: In erythema chronicum migrans (Lipschütz) one finds a single lesion extending peripherally, which does not form gyrate lesions and does not break up into numerous lesions; it remains single. Whereas numerous lesions

occur in erythema annulare centrifugum, in erythema chronicum migrans, one, and occasionally two, lesions only are found on the lower extremities.

DR. EUGENE F. TRAUB (by invitation): Cases of erythema annulare centrifugum have been thoroughly investigated in the past for any possible cause, and as a rule none is to be found. In other words, foci of infection, allergies and the like, have been suspected, but never proved, to be causes in these cases.

DR. JACK WOLF: Yes, that is true.

A Case for Diagnosis (Psoriasis?). Presented by DR. ANTHONY C. CIPOLLARO.

M. L., a salesman aged 41, first consulted the presenter on Jan. 9, 1945. A lesion had developed on the glans penis about three years before. It had healed completely for a time, but about a year ago it recurred and has been present ever since. The patient has been treated with various topical remedies, soothing as well as stimulating, with smallpox vaccine, roentgen rays, grenz rays and ultraviolet radiation. He has been given nicotinic acid by mouth, liver extract by intramuscular injection and calcium by mouth. Friction has been avoided for months at a time. The affected area is constantly covered with a gauze bandage and soothing emollients, lotions, emulsions and the like. The eruption has remained unchanged.

The glans penis shows an exudative, scaly, erythematous and fissured eruption. At times the itching is intolerable. The eruption is now more extensive and exudative than it was originally. The only topical remedy which seems to reduce the exudation and relieve the burning and itching is "noxzema" (a proprietary preparation containing camphor, menthol, phenol, lime water, oil of cloves and oil of eucalyptus in a greaseless base).

DISCUSSION

DR. ISADORE ROSEN: I have had occasion to see this patient several times before, when the features of the eruption were much severer. The diagnostic possibilities are chronic exudative dermatitis (contact), psoriasis and so-called erythroplasia. I do not think it is the disease last named, as its clinical features do not coincide with the course of the disease in this case.

DR. FRED WISE: I am not able to offer a clinical diagnosis and believe that a biopsy is indicated, to exclude or confirm the diagnosis of balanitis, psoriasis or erythroplasia of Queyrat.

DR. SAMUEL M. PECK: I have had poor results in treating such patients. I have turned some of them over to Dr. Sachs, because he has developed an apparently successful therapy. I do not believe that the eruption in this case is either psoriasis or erythroplasia; in my opinion, it is a type of chronic balanitis, but I know of no therapy which has been successful.

DR. WILBERT SACHS: It is of little value to discuss therapy until a diagnosis is established. I would suggest the diagnosis of erythroplasia. A biopsy would corroborate this or would exclude other dermatoses, such as psoriasis.

DR. DAVID BLOOM: Although the lesion does not present the typical features of erythroplasia, a biopsy is necessary to exclude this possibility. Like Dr. Scheer, I have seen eczematoid lesions on the penis which proved to be erythroplasia.

DR. HERMAN SHARLIT: Some day, after he has done all he can, some dermatologist will have the courage to place one of these patients in the hands of a clever psychiatrist.

DR. E. W. ABRAMOWITZ: I do not think this eruption is due to a drug. The patient says he is taking nothing but aluminum hydroxide gel. The only drug I know of which could cause this localized dermatitis of the glans penis would be methenamine. The eruption looks like psoriasis. I should like to ask whether any one has seen a case in which erythroplasia turned into cancer.

DR. GEORGE C. ANDREWS: Has the urine been examined?

DR. ANTHONY C. CIPOLLARO: It has repeatedly been found to be normal.

Lupus Erythematosus. Presented by DR. MAX SCHEER.

C. P., a woman aged 36, is presented from the Skin and Cancer Unit of the New York Post-Graduate Hospital with an eruption on the face of two years' duration.

The eruption covers the entire face in masklike fashion, sparing the eyelids and the alae of the nose. The lesions are confluent, flat, indurated and bright red. Telangiectasis; small, yellowish, adherent scales, and dilated follicles are present.

The patient states that this eruption appeared during the time she was employed as a welder, using a blowtorch, which produces a continuous ultraviolet flash.

The histologic picture confirms the clinical diagnosis of lupus erythematosus.

DISCUSSION

DR. HERMAN SHARLIT: I should like to ask whether lupus erythematosus is a recognized hazard of the welding industry. A certain amount of protection is to be had from goggles.

DR. SAMUEL M. PECK: That industry knows the hazard well and takes good care of its people. I have never been in a plant where workers did not have some protection. I asked the patient whether she was a welder's helper, for the helper wears only goggles and is therefore the one who gets the maximum exposure. The welder himself wears heavy canvas gloves, an apron and a plastic hood extending well down on the chest.

DR. GEORGE C. ANDREWS: One other question comes to mind. What was the patient's diet and state of nutrition before this actinic exposure?

DR. MIHRAN B. PAROUNAGIAN: I agree with the diagnosis. A number of cases of lupus erythematosus have occurred on exposure to sunlight.

DR. SAMUEL M. PECK: The patient says that her welding was performed with a blowtorch. I think it is important to state in the record just what she was doing. This case would be the first I have heard of in which the eruption could be traced to ultraviolet light from a welding arc.

DR. EUGENE F. TRAUB: Dr. George M. Lewis showed a case at a meeting of the New York Dermatological Society in which a similar sequence of events was said to have occurred, but there was the same question of protection. These welders frequently work on the decks of ships or out of doors; they may take off their masks and get a natural sunburn, and the welding may not be a factor at all.

DR. ANTHONY C. CIPOLLARO: It is a question in my mind whether welding has anything to do with lupus erythematosus. I think this patient has lupus erythematosus, and if welding has anything to do with it, this factor should furnish a clue to the cause of lupus erythematosus. The consensus now is that lupus erythematosus is of infectious, rather than actinic, origin.

DR. HERMAN SHARLIT: You do not believe that actinic rays have anything to do with precipitating the eruption?

DR. ANTHONY C. CIPOLLARO: Actinic rays might be a precipitating or an additive cause, but I feel that lupus erythematosus is of infectious origin.

DR. DAVID BLOOM: Was the patient exposed to much heat during her work as a welder?

DR. E. W. ABRAMOWITZ: Lupus erythematosus has been reported in the literature as occurring after burns and other injuries. The Viennese school particularly, and I believe the French school too, still believe that lupus erythematosus of the discoid type is of tuberculous origin in most cases. However, the incidence of tuberculosis in Europe renders judgment on that point difficult. The English and Americans believe that some other cause is operative in most cases of lupus erythematosus. This patient has lupus erythematosus. It might be difficult to disprove that her occupation was not causally related to her eruption.

Scleroderma. Presented by Dr. Fred Wise.

I. G., a man aged 42, was previously presented at the New York Dermatological Society on Oct. 23, 1945. Beginning on November 1, he was given tablets of calcium penicillin, containing 20,000 units each, at three hour intervals, one-half hour before meals, for six days.

DISCUSSION

Dr. George C. Andrews: I gave penicillin to 2 patients who had a severe and extensive, progressive type of scleroderma. One was a nurse who had previously been thoroughly studied at Mount Sinai Hospital, where she had been in bed for some time. Before I began penicillin therapy, her fingers were almost rigid, and she was not able to use them except as claws. I gave her two courses of penicillin, each one totaling 3,000,000 to 4,000,000 units, in daily doses of 300,000 to 400,000 units for ten days, intramuscularly. Before she left the hospital she was able to do some knitting. She is now actively working as a public health nurse. The other patient, also at Presbyterian Hospital, had a course of 3,000,000 or 4,000,000 units, with great improvement. Later, this patient had another course of penicillin under another physician. I have now lost track of her.

Dr. E. W. Abramowitz: I have recently seen more cases of scleroderma than in former years. The condition of some of the patients is so pitiable that if any money is available for research this disease should receive preference. Physicians interested in peripheral vascular disease see more cases than do we dermatologists, and they are discouraged with present methods of treatment, particularly of patients with systemic involvement. My last patient had stricture of the esophagus and died of cardiac failure. A patient on Dr. Rosen's service who was thought to have scleredema is getting physostigmine bromide, 15 mg. tablets, with apparent improvement. Another patient on Dr. Rosen's service had morphea-like lesions on her left leg. The lesions softened after treatment with physostigmine for one year. Dr. Cipollaro tells me he has had encouraging results with sodium nitrite. Men who have had wide experience with peripheral vascular diseases think none of the vasodilator drugs has any value in treatment of scleroderma.

Dr. Fred Wise: Of course the prognosis in the present case is extremely poor, no matter what treatment is administered.

Squamous Cell Epithelioma of the Lower Lip with Possible Regional Metastasis. Presented by Dr. Fred Wise.

N. S., a man aged 53, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Oct. 27, 1945, complaining of lesions of two and a half months' duration. He stated that three months ago a pair of pliers fell on his mouth, cutting his lip.

The patient has an extensive induration on the left side of the lower lip about 3 cm. in diameter. On the external surface of the lip there is a lesion 2 cm. in diameter with a central conical depression. On the inside of the lip the mucous surface is irregularly ulcerated, the greatest diameter of the area being 3 cm. There are a palpable submental lymph node 1 cm. in diameter and a questionably enlarged submaxillary node on the left side.

Routine laboratory tests gave normal results. The discharge from the lesion expressed on a slide and stained with the Ziehl-Neelsen method was negative for Mycobacterium tuberculosis.

A histologic section, examined by Dr. Charles F. Sims, was diagnosed as "prickle cell epithelioma."

The lesion was excised at the tumor clinic of the Skin and Cancer Unit. The specimen, a V-shaped excision of part of the lower lip, was examined by Dr. A. E. Margulis and interpreted as "squamous cell carcinoma of the skin and mucous membrane, grade I." The section showed a malignant squamous cell neoplasm arising from both the skin and the mucous membrane, at the mucocutaneous junction, and infiltrating the tunica propria and the muscle of the lip deeply, passing

across the lip and connecting with the epithelium of the mucous membrane of the oral surface of the lip. The tumor was composed of multiple, irregular nests, both small and large, of well differentiated, often keratinizing, squamous cells, with a few mitotic figures. The surface was highly irregular, with projections and depressions, and was filled with keratin. There were extensive fibrosis and diffuse chronic inflammation around the infiltrating tumor. The growth did not reach the planes of surgical excision at any point and appeared locally to have been completely excised.

The patient was advised to return to the hospital two weeks later for a dissection of the neck.

DISCUSSION

DR. HERMAN SHARLIT: It is interesting to what extent one can feel satisfied with the supposition that injury played a real and effective part in the genesis of this tumor; on the other hand, one wonders whether an accident which occurred several weeks before was not just coincidental. Can injury produce cancer? The man is convinced that he received a severe injury in that exact location and that a fulminating cancer developed within a short time.

DR. GEORGE C. ANDREWS: From all that I have read or been taught by Dr. James Ewing or Dr. Francis Carter Wood, I have always been of the opinion that trauma is seldom the cause of carcinoma. It may be a cause of some sarcomas. However, chemical irritation frequently seems to favor the growth of cancer. It is possible, of course, that ideas have changed in the past few years, but I had not heard of it. Dr. Wolf says that the role of trauma was accepted in his cases. Will he tell us who accepted the traumatic origin?

DR. JACK WOLF: It is always difficult, if not altogether impossible, to establish causal relations in a rapidly growing lesion. There have now been enough reliable reports of cases which have followed an acute injury to leave little doubt that acute injury may occasionally cause cancer. I have 2 personal cases in mind, 1 in which a piece of metal was lodged subcutaneously over the bridge of the nose, with a basal cell epithelioma developing in the course of the next few months at the site of injury, and another in which a basal cell epithelioma of the cheek followed a burn produced by a hot "scale."

DR. MIHRAN B. PAROUNAGIAN: I have always understood that trauma was the cause of cancer in a considerable number of cases. Not long ago I saw a man who cut himself with a razor blade on the malar process, as a result of which he presented a definite cancerous lesion.

DR. ISADORE ROSEN: There is something unusual and striking about the lesions. If I knew nothing of the history, I should undoubtedly make a diagnosis of multiple gumma. I feel that it would be advisable to treat this patient with three or four intramuscular injections of bismuth subsalicylate 10 per cent emulsion in peanut oil and oral administration of potassium iodide before more radical surgical procedures are instituted.

DR. ANTHONY C. CIPOLLARO: I should like to elaborate on the statement that chemical trauma may have something to do with cancer and, in support of that idea, to cite the case of a man with an epithelioma of the lower lip. He also had syphilis and was treated for two or three weeks with arsenicals, by which time the lesion had become four to six times as large as it originally was. Most of the men who saw this patient thought arsenic had something to do with the rapid growth.

DR. SAMUEL B. PECK: I think we ought to bring up for discussion this question of the relation of trauma to carcinogenesis. Throughout all industries one has definite proof that certain of the coal tar products and certain of the petroleum hydrocarbon products will cause cancer. Certain industrial methods are known to produce carcinoma of the bladder, so that all workers are required to have cystoscopic examinations at intervals. It is not so much the irritation which is responsible for cancer as a specific effect, probably due to a definite chemical structure.

DR. FRED WISE: Confining my comments to the case under discussion, I believe the evidence is much in favor of the cancer following trauma. The man gives a clear history of trauma, followed two and one-half months later by the appearance of a growth and perforation of the lip. An important point is the differentiation of trauma of recent occurrence and trauma of previous long standing. In this case the trauma was of recent occurrence, and for that reason the patient is presented for consideration as to diagnosis and treatment.

A Case for Diagnosis (Congenital Hypotrichosis and Keratosis Pilaris?).
Presented by DR. DAVID BLOOM.

M. F., a man aged 27, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital complaining of an eruption on the face of a few years' duration, and of alopecia of the scalp and an eruption on the body which have been present since early childhood.

On the upper lip and the chin the patient presents an erythematopustular eruption. The bearded region shows sparse hair and numerous keratotic follicular papules. Similar lesions are also seen on the thighs, abdomen, chest and arms. There is complete alopecia of the scalp in the middle zone, extending from the forehead to the occipital region. The hair on the sides of the scalp is sparse, and there are scaling and folliculitis in these areas. The hair in the axillas and the pubis is sparse.

The patient states that the alopecia and the keratosis pilaris on the body have been present as long as he can remember. The family and past personal histories were essentially unremarkable, except for frequent eruptions in the summer.

Microscopic examination of the hair of the scalp revealed no abnormality.

DISCUSSION

DR. HERMAN SHARLIT: I saw this man at the clinic and asked him whether he had ever had roentgen irradiation of his scalp; he said he had, twenty years ago. This factor in the history should be taken into account.

DR. JACK WOLF: If this man received an overdose of roentgen radiation to the scalp, the clinical picture in that location could be explained on that basis. The rest of the clinical picture is only an exaggerated form of keratosis pilaris with involvement of the cheeks, chest and scalp. On the cheeks the process has gone on to the end stage, with loss of the hyperkeratotic follicular plugs and resulting atrophy of the follicles. In the end stage the cheeks remain red. The syndrome of keratosis pilaris with such involvement of the cheeks is referred to by the French as "keratosis pilaris rubra atrophicans facies." I believe the involvement of the upper and lower lips is a complicating folliculitis or an early sycosis.

DR. SAMUEL M. PECK: I agree with Dr. Wolf that the clinical picture is that described by the French school as a keratosis followed by atrophy, but the patient shows two features which I often see after keratosis follicularis. There is a peculiar involvement of the lip, which does not resemble sycosis but is more like seborrhea; this may also be seen on the eyelids. This develops during hot, humid weather; and exposure to sunlight is also a precipitating factor. The lesion does not respond to administration of vitamin A. We now have under observation at Mount Sinai Hospital a mother and daughter with keratosis follicularis. Mere exposure of the daughter's back to large doses of ultraviolet radiation produces a weeping eczematoid eruption which, if it were on the face, one would think was seborrheic dermatitis. I think the case presented tonight would be interesting to study from the viewpoint of vitamin A deficiency. It may well fit into the group of vitamin A dysvitaminoses.

DR. ISADORE ROSEN: When I first saw this man at the clinic, my impression was that he might have a mild form of monilethrix, but this diagnosis was ruled out by the absence of beaded hairs on microscopic examination. The feature which suggested monilethrix was an associated keratosis pilaris over the neck, scalp and face. I believe the condition belongs to the group of congenital ectodermal defects.

DR. E. W. ABRAMOWITZ: To me the disease in this case looks like ulerythema sycosiforme. The patient had some form of treatment to the scalp when a child, possibly roentgen therapy. The bearded region of the face shows an erythematous and pustular folliculitis, which may be an extension of the old cutaneous involvement of the scalp.

DR. JACK WOLF: I think that the disease is nevoid. If it appears chiefly in females, and is sharply limited to the cheeks, is it likely to have anything to do with malformation of the hair?

DR. WILBERT SACHS: The process is generalized. It may be a congenital malformation of the hair follicles and the hair. The sebaceous glands would thus be involved, and that would account for the sebaceous element that is present.

DR. DAVID BLOOM: The patient presents complete alopecia in the central portion of the scalp and sparse growth of hair on the lateral aspects of the scalp. On the body he shows generalized keratosis pilaris, and many of these papules are pierced by a hair. This congenital hypotrichosis belongs to the minor ectodermal defects which are inherited in a dominant mode. No similar abnormality could be found in any other member of the family. The patient also presents sycosis vulgaris of the bearded region, which was benefited considerably by the application of a penicillin ointment.

CLEVELAND DERMATOLOGICAL SOCIETY

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Nov. 29, 1945

Tuberculosis Verrucosa Cutis of the Neck. Presented by DR. W. W. MURPHY and DR. B. HELD.

Diffuse Idiopathic Atrophy of the Skin Associated with Advanced Pulmonary Tuberculosis. Presented by DR. W. W. MURPHY and DR. B. HELD.

V. S., a white man aged 28, whose paternal grandparents had had asthma, noticed an erythematous lesion on the left shin in 1935. Over a period of several months this lesion thickened, became scaly and finally resolved, leaving an area of atrophic skin. New lesions gradually appeared, enlarged and then coalesced to involve large areas of both lower extremities. In 1942 the forearms and arms became involved in a similar process, while the skin of the lower extremities became more atrophic. Recently the skin of the upper part of the trunk has become involved. For several years the patient has noticed dryness and scaling of the skin of the scalp, face, trunk and soles. The body and pubic hair has fallen; cutis anserina does not occur, and perspiration appears only on the face, palms and soles.

The skin shows a generalized symmetric eruption, most evident on the extensor surfaces of the extremities. The principal lesion is now seen around the shoulder girdle and on the neck and chest and consists of multiple plaques, varying from 1 to 5 cm. in greatest diameter. On the extensor surfaces of the upper extremities are reddish brown areas, varying in size from 2 cm. to large patches on the arms and characterized by atrophy with prominence of the underlying vessels. In some areas the borders can be seen as moderately infiltrated, erythematous bands, about 1 cm. wide, separating the atrophic areas from the adjacent skin. On both lower extremities, from the dorsa of the feet to above the knees, are diffuse areas of brown, atrophic skin, which is thin, without adnexa, loose and covered with thin, dark brown scales, 1 cm. in thickness. Around the knees the skin is thrown into many fine, soft, inelastic folds. The skin of the trunk, face, scalp, palms and soles is dry and shows fine scaling. The body and pubic hair is absent. There is

generalized lymphadenopathy, characterized by flat, firm, nontender, somewhat adherent nodes.

The Kline reaction of the serum was negative. The hemogram and the results of urinalysis were normal.

DISCUSSION

DR. E. W. NETHERTON: This case seemed to me to be one of exfoliative dermatitis. Even though atrophy is extensive, there is much exfoliation. The patient has active tuberculosis; one wonders whether the tuberculosis is not a factor in the exfoliative process, even though the cutaneous lesions preceded the manifest pulmonary tuberculosis.

Dr. R. E. BARNEY: In addition to the more or less generalized eruption, there were an infiltrated plaque over the right clavicle and some infiltrated nodules on the neck. I believe that tuberculosis plays an important part in the generalized scaly, atrophic dermatitis. I think one may regard this process as a type of pityriasis rubra (von Hebra) occurring on the basis of tuberculosis, keeping in mind that it may have a leukemic basis. It would be helpful to obtain a biopsy of the two types of cutaneous lesions.

DR. W. W. MURPHY: The patient refuses to permit a biopsy of the skin.

DR. H. N. COLE: Several years ago Dr. Driver and I admitted a patient with exfoliative dermatitis to the University Hospitals. Biopsy of specimens of skin revealed the picture of tuberculosis. Large numbers of tubercle bacilli were found in the skin. I think a similar picture may be present in this case, particularly over the clavicles. The atrophic areas could represent an idiopathic type. One sees such atrophy with several other systemic diseases, and I do not see why tuberculosis could not produce it.

DR. J. R. DRIVER: About six months later the patient to whom Dr. Cole refers died of fulminating miliary tuberculosis. I think an attempt should be made to determine the type of tuberculosis which this man has—whether human, avian or bovine. I am of the opinion that it is not human tuberculosis, but avian or bovine.

DR. G. A. DE OREO: Another possible etiologic factor is the lymphadenopathy. The posterior cervical chain of superficial lymph nodes on the left side was most easily demonstrable. He may have tuberculous foci of other parts of the reticuloendothelial system, perhaps of the spleen.

A Case for Diagnosis (Mycosis Fungoides?). Presented by DR. W. W. MURPHY and DR. B. HELD.

Mycosis Fungoides. Presented by DR. W. W. MURPHY and DR. B. HELD.

Rhinoscleroma. Presented by DR. W. W. MURPHY and DR. B. HELD.

M. S., a white woman aged 53, born in Poland, was brought to Cleveland City Hospital in January 1943, for involutional psychosis of paranoid type. At this time there was a small, crusted lesion on the right side of the cartilaginous septum of the nose. This lesion has slowly enlarged.

Examination reveals a sharply defined, firm, pink, crusted tumor extending 5 mm. below, into and occluding the right nostril. It appears to originate from the septum. There is a slight mucopurulent exudate.

The urine was normal. The Wassermann and Kline reactions of the serum were negative. The hemogram was normal. Culture of material from the right nostril yielded gram-positive bacilli and Staphylococcus aureus. Histologic examination revealed elongated, anastomosing stratified epithelial cells, forming a framework. Within the interstices was infiltration with lymphocytes, Mikulicz cells, neutrophils and plasma cells. There were also numerous acidophylic, hyaline degenerated cells of Pallizari.

Roentgen therapy is being given. Sodium penicillin, 15,000 units every three hours for two weeks, has been administered. No change has been noted.

DISCUSSION

DR. H. HECHT: This disease is rare in the United States. Years ago I saw a few cases in Prague. The microscopic picture was typical. I remember 2 cases in which the larynx was infiltrated. Treatment is not satisfactory. One may remove the lesion surgically or try roentgen therapy.

DR. R. E. BARNEY: Had there been a lesion on the other side of the lip, involving the mucous membrane of the left naris? There was a small area on the upper lip which looked like the scar of a surgical incision. Had a process been present and healed?

DR. W. W. MURPHY: So far as we have been able to learn, the lesion on the right side is the original and only one. The growth first appeared about two years ago, when the patient was sent to City Hospital from Cleveland State Hospital. At that time it was described as a small, wartlike lesion. Over the intervening period it has developed to its present size.

DR. E. W. NETHERTON: Rhinoscleroma is described as hard, firm and woody, features absent in this case. Is this common?

DR. H. HECHT: Most such lesions are very hard.

DR. W. W. MURPHY: Cunning and Guerry (Scleroma, *Arch. Otolaryng.* **36**:662 [Nov.] 1942) reported approximately 106 cases from the United States and Canada. Of the patients 16 were born in the United States, most of them coming from eastern or southeastern Europe. At the International Congress of Otology, Rhinology and Laryngology held in Madrid, Spain, in 1932, an extensive survey was presented. Belinoff reported 2,351 cases up to that time. The disease occurs more frequently in women. It is most common in the nose and larynx. It is chronic and may be fatal, usually by obstruction.

Lichen Nitidus. Presented by DR. W. W. MURPHY and DR. B. HELD.

Fibrosarcoma of the Heel. Presented by DR. W. W. MURPHY and DR. B. HELD.

Fox-Fordyce Disease in a Girl Aged Twelve and One-Half Years. Presented by DR. BENJAMIN P. PERSKY.

Lupus Erythematosus with Chrysiasis. Presented by DR. DON R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER.

Book Reviews

The X-Ray Treatment of Accessible Cancer. By D. Waldron Smithers, M.D. Price, $8.50. Pp. 147, with 101 illustrations, including colored plates, diagrams, charts, 21 tables and 12 graphs. Baltimore: Williams & Wilkins Company, 1946.

This volume is a compilation of the author's personal experiences with the roentgen ray treatment of malignant diseases of the skin and adjacent mucous membranes. Like other workers in this field, the author believes that with a combination of surgical treatment and radiotherapy it should be possible to cure all cases of accessible cancer. He discusses the merits of both surgical and radiation therapy but concludes that for several reasons roentgen radiation properly applied is superior to surgical treatment in most instances.

Two procedures described in detail are noteworthy. The first of these is the utilization of tumor cell counts to follow the progress of the response of the neoplasm to radiotherapy. Serial biopsies are performed before radiation and at intervals during radiation, daily at first and at longer intervals as the tumor recedes. The numbers of the differentiating, resting, degenerating and mitotic cells are plotted on graph paper, and curves are drawn. Mitotic cells disappear within a few days after radiation is begun. As a result of the radiation the degenerating cells gradually increase in number, the resting cells decrease, and, during the period of recovery from the effects of radiation, the differentiating cells gradually increase. These changes are well illustrated with colored photographs and charts.

The other notable procedure is the logical utilization of radiations of different wavelengths to distribute the maximum effect of the radiations as evenly as possible throughout the tumor mass. Most dermatologists and radiologists employ approximately the same quality of radiation throughout the treatment of a particular neoplasm. Smithers usually begins by using 200 kilovolt apparatus and then changes to 100, 60 or 45 kilovolt apparatus. In many instances 6,000 to 8,000 r are administered in about eighteen days.

The classification of accessible cancer is the usual one, but the division of the extent of the disease into stages is another new idea. Staging helps physicians to select the proper therapy and to foretell changes in the tumor and in the condition of the patient.

Concise and well illustrated, the book includes eleven chapters, an appendix containing definitive terms and useful isodose curves, a bibliography and author and subject indexes. The paper, printing and illustrations are of fine quality.

This work should be in the library of all who are interested in the problem of cancer and should be particularly valuable to any one using roentgen rays for the treatment of malignant diseases of the accessible parts of the body.

News and Comment

GENERAL NEWS

Application for Space in Scientific Exhibit.—Fellows of the American Academy of Dermatology and Syphilology who wish to apply for space in the Scientific Exhibit at the Chicago meeting of the academy in December 1947 are requested to write for an application blank to Dr. Marcus R. Caro, 25 East Washington Street, Chicago 2, Illinois.